Facultad de Ciencias

Departamento de Química Orgánica

Novel Ni-Catalyzed Cross-Coupling and Cascade Cyclization-Coupling Reactions for the Formation of $C–C_{alkyl}$ Bonds

TESIS DOCTORAL

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Madrid, diciembre de 2009

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PRÓLOGO

Esta memoria recoge el trabajo y los resultados obtenidos a lo largo de la realización de la Tesis Doctoral. El manuscrito incluye una *Introducción* que consta de dos apartados; el primero de ellos describe, por supuesto de una forma muy breve, el origen y la evolución de algunas de las reacciones basadas en el acoplamiento cruzado y catalizadas por metales de transición de más amplia aplicación en la formación de enlaces C–C. Se presta especial atención a las reacciones de Negishi y de Kumada, más directamente relacionadas con la línea de investigación en la que se enmarca el trabajo realizado. Un segundo apartado trata, de forma más específica, las reacciones de acoplamiento cruzado catalizadas por níquel en las que intervienen como nucleófilos, fundamentalmente, reactivos de organozinc o magnesianos.

El apartado de *Discusión de resultados* se divide en tres secciones principales donde se exponen los resultados obtenidos en las reacciones de acoplamiento cruzado catalizadas por níquel. En un primer apartado se recogen las condiciones experimentales para la formación de enlaces $C(sp^2)$–$C(sp^3)$, empleando haluros de arilo, heteroarilo o alquenilo y reactivos de alquilzinc. La segunda sección recopila los resultados obtenidos en los ensayos para la formación de enlaces $C(sp^3)$–$C(sp^3)$ mediante el acoplamiento cruzado de haluros de alquilo con haluros de alquilzinc o alquilmagnesio. El tercer apartado describe el desarrollo de un proceso de ciclación y acoplamiento en cascada que transcurre fácilmente, con buenos rendimientos y en condiciones de reacción suaves, permitiendo de este modo la formación conjunta de dos nuevos enlaces $C(sp^3)$–$C(sp^3)$. En cada uno de los apartados mencionados se subrayan las ventajas que presenta el procedimiento, no sólo desde el punto de vista económico y sintético, por su versatilidad y aplicabilidad, sino desde el punto de vista metodológico. En este sentido, además de recoger los resultados y los datos más relevantes del trabajo, se presentan las diferentes propuestas mecanísticas y las aportaciones más novedosas, fruto de la investigación tanto en el campo experimental como en el computacional, que han proporcionado un conocimiento más profundo sobre el transcurso de los procesos mencionados.

En el trabajo de investigación recopilado en la primera sección se contó con la colaboración de Manuel Guisán Ceinos y en el de la tercera sección con Miguel García Iglesias. Además, el trabajo recogido en esta última sección permitió la consecución del Diploma de Estudios Avanzados.

Los estudios computacionales han sido realizados por los directores de este trabajo.

Hasta el momento de redactar esta memoria, el trabajo realizado a lo largo de los años de realización de esta Tesis Doctoral ha dado lugar a las siguientes publicaciones:

- *"Ni-Catalyzed Cascade Formation of C(sp^3)−C(sp^3) Bonds by Cyclization and Cross-Coupling of Iodoalkanes with Alkylzinc Halide"*
  Phapale V. B.; Buñuel E.; García-Iglesias M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.

- *"Nickel-Catalyzed Negishi Cross-Coupling Reactions: Scope and Mechanisms"*
  Phapale, V. B.; Cárdenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598-1607.

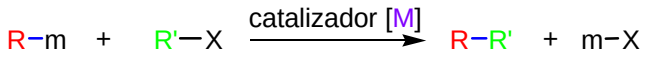
- *"Nickel-Catalyzed Cross-Coupling of Alkylzinc Halides for the Formation of C(sp^2)-C(sp^3) Bonds: Scope and Mechanism"*
  Phapale, V. B.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D. J. *Chem. Eur. J.* **2009**, DOI: 10.1002/chem.200901913.

RESUMEN

†La continua búsqueda de moléculas biológicamente activas es una de las áreas de investigación más extensas en la cual la química orgánica juega un papel fundamental. Ya que la mayoría de estas moléculas, incluso los productos naturales de uso comercial, se sintetizan en laboratorio existe una constante demanda de nuevos métodos para la construcción selectiva de enlaces C–C. Además, la química de materiales requiere, cada vez más, procedimientos efectivos para la construcción de las nuevas moléculas diseñadas a medida que respondan a las nuevas necesidades del mercado. Idealmente dichos procedimientos deberían transcurrir en condiciones suaves, siendo tolerantes con un amplio abanico de grupos funcionales. Al mismo tiempo, la formación de nuevos enlaces de manera quimio-, regio- y estereoselectiva se ha convertido en uno de los principales objetivos de la química orgánica.

Los compuestos organometálicos presentan ciertas propiedades estructurales que los han convertido en reactivos insustituibles en el desarrollo de nuevos métodos para la formación enlaces C–C. Así, la polaridad del enlace carbono–metal confiere al carbono unido al metal un carácter nucleófilo que posibilita su reacción con una gran variedad de electrófilos y la obtención de los productos resultantes del acoplamiento cruzado.

La reacción de acoplamiento cruzado de reactivos organometálicos con electrófilos orgánicos en presencia de catalizadores que contienen metales pertenecientes a los grupos 8-10 del sistema periódico, en particular níquel y paladio, resulta uno de los métodos más frecuentemente seleccionados para la formación de una gran variedad de enlaces C–C.[1] Estas reacciones, actualmente accesibles con una amplia gama de reactivos organometálicos y electrófilos, constituyen hoy en día una clase común de transformaciones sintéticas (**Esquema I**).



m = Si, B, Sn, Al, Zn, Zr, Mg.....
X = I, Br, Cl, OTf.....
M = Fe, Ni, Cu, Pd, Rh.....

Esquema I

† En este resumen se ha respetado la numeración de los compuestos tal y como aparece en los capítulos siguientes. La numeración de las referencias bibliográficas es, sin embargo, independiente del resto de las secciones que componen esta memoria.

[1] (a) *Metal-catalyzed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **1998**. (b) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **2004**.

La reactividad de las especies organometálicas frente a los electrófilos aumenta con el carácter iónico del enlace carbono–metal. Consecuentemente, es posible hacer una clasificación de las reacciones de acoplamiento cruzado catalizadas por metales de transición de acuerdo con la especie organometálica empleada como nucleófilo. Atendiendo a esta clasificación, cada protocolo ha recibido el nombre del investigador principal responsable de su descubrimiento y posterior progreso. Así, el acoplamiento de Negishi puede definirse vagamente como el acoplamiento cruzado catalizado por Ni o Pd que emplea compuestos organometálicos con metales de electronegatividad intermedia, tales como Zn, [2,3,4,5,6,7,8] Al y Zr.[9,10,11,12] Otro ejemplo es el de la reacción de

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[2] (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348. (b) Knochel, P.; Yen, M. C. P.; Berk, S. C.; Yalbert, J. *J. Org. Chem.* **1988**, *53*, 2390-2392.

[3] Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117-2188.

[4] Algunos ejemplos recientes: (a) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G.; *Tetrahedron*, **1996**, *52*, 7201-7220. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724. (c) Kabir, M. S.; Monte, A.; Cook, J. M. *Tetrahedron Lett.* **2007**, *348*, 7269-7273.

[5] Algunos ejemplos recientes de acoplamiento cruzado $C(sp^2)$–$C(sp^2)$ catalizado por Pd: (a) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2723. (b) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028-13032. (c) Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593-2595. (d) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *Org. Lett.* **2008**, *73*, 7380-7382. (e) Manolikakes, G.; Dong, Z.; Mayr, H.; Li, J.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 1324-1328.

[6] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527-12530.

[7] (a) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *113*, 7027-7028. (b) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 231-232. (c) Stadtmüller, H.; Vapuel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204-1220.

[8] Ejemplos recientes de acoplamiento de haluros de arilo y haluros de alquilzinc: (a) Bartrum, H. E.; Adams, H.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 3701-3712. (b) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923-3925. (c) Liu, Q.; Duan, H.; Luo, X.; Tang, Y.; Li, G.; Huang, R.; Lei, A. *Adv. Synt. Catal.* **2008**, *350*, 1349-1354. (d) Wang, H.; Liu, J.; Deng, Y.; Min, T.; Yu, G.; Wu, X.; Yang, Z.; Lei, A. *Chem. Eur. J.* **2009**, *15*, 1499-1507. (e) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532-7533.

[9] (a) Baba, S. Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731. (b) Negishi, E.; Baba, S. *J. Chem. Soc. Chem. Comm.* **1976**, 596-597.

[10] Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531-1534.

[11] Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82-83.

[12] Wang, G.; Zhu, G.; Negishi, E. *J. Organomet. Chem.* **2007**, *692*, 4731-4736.

Kumada-Tamao que consiste en el empleo de nucleófilos que contienen Mg.[13, 14,15,16,17,18]

Obviamente, el carácter menos básico y nucleófilo del reactivo permite que los acoplamientos cruzados transcurran con una quimioselectividad mayor. El uso de especies altamente reactivas, como organolíticos, compromete a menudo la selectividad y la tolerancia con respecto a grupos funcionales sensibles. Por otro lado, la reacción de las especies organometálicas menos reactivas, tales como compuestos de organozinc, organoestannanos u organoboranos, debe promoverse necesariamente mediante el uso de catalizadores de metales de transición. Se trata, por tanto, de conseguir el compromiso más favorable entre nucleofilia y selectividad, desarrollando procesos en los que intervengan especies suficientemente reactivas frente a una extensa variedad de electrófilos y con una marcada tolerancia frente a grupos funcionales sensibles.[19]

La reacción de acoplamiento cruzado catalizada por metales de transición ocurre a través de una serie de pasos secuenciales, tal como se refleja en el **Esquema II** que se recoge a continuación.[1,20]

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[13] (a) Tamao, K; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. (b) Tamao, K; Zembayashi, M.; Kiso, Y.; Kumada, M. *J. Organomet. Chem.* **1973**, *55*, C91-94. (c) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180-186.

[14] Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, *3*, 144-145.

[15] Terao, J; Kambe, M. *Acc. Chem. Res.* **2008**, *41*, 1545-1554.

[16] Hayashi, T. *J. Organomet. Chem.* **2002**, *653*, 41-45.

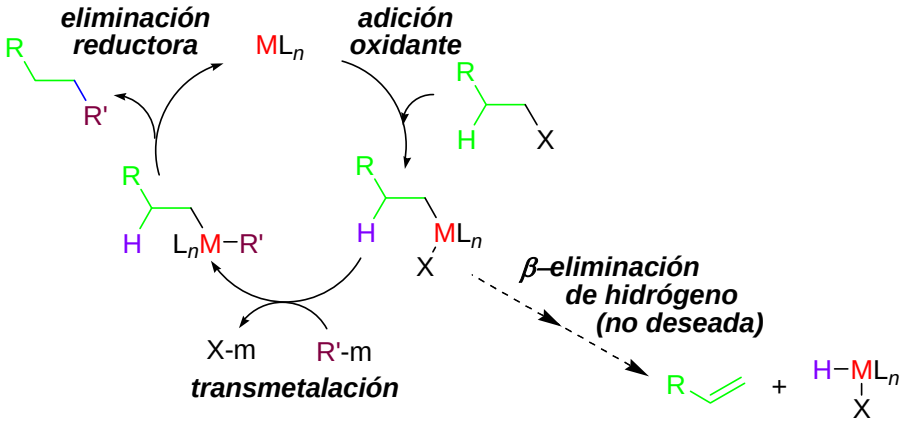
[17] Algunos ejemplos recientes: (a) Zhang, L.; Cheng, J.; Zhang, W.; Lin, B.; Pan, C.; Chen, J. *Chem. Comm.* **2007**, *37*, 3809-3814. (b) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162-167. (c) Manolikakes, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 205-209. (d) Gu, S.; Chen, W. *Organometallics*, **2009**, *28*, 909-914. (e) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844-3845. (f) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364-9370.

[18] Gauthier, D.; Beckendorf, S.; Gogsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536-3539.

[19] *Handbook of Functionalized Organometallics*, Knochel, P.; Krasovskiy, A; Sapountzis, I. Wiley-VCH, Weinheim, **2005**, *1*, 109.

[1] (a) *Metal-catalyzed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **1998**. (b) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **2004**.

[20] (a) Cárdenas, D. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3018-3020. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852-860.



Esquema II

Los tres pasos son procesos perfectamente conocidos en catálisis homogénea,[21] aunque la transmetalación sea la etapa menos conocida ya que es altamente dependiente de la naturaleza del reactivo organometálico y de las condiciones de reacción.

Los metales de transición del grupo 10, en concreto níquel y paladio, resultan muy efectivos catalizando este tipo de reacciones. Además, para el ensamblaje de nuevos enlaces C–C es posible emplear una gran diversidad de reactivos organometálicos y electrófilos orgánicos, incluidos los que contienen radicales alquilo, arilo, alquenilo y alquinilo.

Sin embargo, todavía existen limitaciones en las posibles combinaciones de los reactivos electrófilos y nucleófilos que intervienen en el acoplamiento.[22] El fracaso relativo que, hasta hace algunos años, venía siendo común en el acoplamiento cruzado de electrófilos alquílicos se ha atribuido a varios pasos problemáticos en el ciclo catalítico general que se ha mencionado anteriormente (**Esquema II**). En particular, en el caso de los complejos de Pd(0) los haluros de alquilo reaccionan lentamente. Además, una vez que el complejo alquil-Pd(II) se ha formado, existe la posibilidad de su descomposición a través de una rápida β-eliminación of hidrógeno. Por otro lado, la eliminación reductora es un proceso lento[23] que en muchos casos puede acelerarse mediante la adición de especies capaces de estabilizar estados de oxidación bajos para el metal, típicamente ligandos con propiedades π-aceptoras.

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[21] *Palladium Reagents in Organic Syntheses*, Heck, R. F., Academic, New York, 1985.

[22] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

[23] Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779-5789.

A pesar de todos estos problemas, hasta el momento se han descrito algunos ejemplos de reacciones de acoplamiento alquilo–alquilo. El acoplamiento de reactivos de Grignard con haloalcanos catalizado por sales de cobre es, probablemente, el más estudiado de estos procesos,[24] aunque el uso de otras especies organometálicas menos reactivas está permitiendo extender el método a la obtención de sustratos altamente funcionalizados. En este sentido, sin embargo, la baja regioselectividad en la reacción de electrófilos alílicos y la lenta eliminación reductora de especies *σ*-alquil-*π*-alil- o di-*π*-alilpaladio[21,25,26] son temas todavía pendientes.

Se han propuesto algunas soluciones al problema de la formación de enlaces alquilo–alquilo. Una de ellas consiste en el empleo de varios ligandos fosfina efectivos en la estabilización de los intermedios de Pd(0) o Ni(0). En muchos casos la trifenilfosfina resulta un ligando satisfactorio, sin embargo se han diseñado nuevos ligandos con el fin de aumentar la eficiencia o la selectividad de los catalizadores y la aplicabilidad del proceso. Con el propósito de minimizar la *β*-eliminación de hidrógeno en los acoplamientos $C(sp^3)$–$C(sp^2)$ de alquilmetales, se han diseñado bisfosfinas que presentan un ángulo P–M–P grande, tales como dppp, dppb y dppf. También se ha descrito la elevada reactividad frente a la adición oxidante de fosfinas voluminosas, tales como $(t\text{-Bu})_3P$, Cy_3P o 2-(di-*t*-butilfosfino)bifenilo, lo que ha facilitado el acoplamiento de cloroarenos con paladio.[27]

Durante los últimos años se han alcanzado importantes logros en reacciones de acoplamiento catalizadas por Ni empleando reactivos de organozinc y organomagnesio como nucleófilos. Además de los acoplamientos que permiten la formación de enlaces C(sp)–C y la proliferación de nuevos procedimientos para la ya conocida formación de enlaces $C(sp^2)$–$C(sp^2)$, se ha producido el desarrollo de nuevos procedimientos para la

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[24] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1483-1487. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351-360.

[21] *Palladium Reagents in Organic Syntheses*, Heck, R. F., Academic, New York, 1985.

[25] Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691-694.

[26] Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620-3628.

[27] (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561. (c) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

formación de enlaces $C(sp^2)$–$C(sp^3)$ y $C(sp^3)$–$C(sp^3)$ que involucran el empleo de electrófilos y/o nucleófilos alquílicos.

En este trabajo, nuestro interés se enfocó en el estudio y desarrollo de reacciones de acoplamiento cruzado catalizadas por Ni que permitieran la formación de los dos últimos tipos de enlace C–C mencionados anteriormente.

Uno de nuestros objetivos consistía, por tanto, en la *formación de enlaces* $C(sp^2)$–$C(sp^3)$ empleando electrófilos $C(sp^2)$. Los acoplamientos de haluros de arilo y haluros de bencilzinc catalizados por Ni ya habían sido descritos por Negishi en las primeras publicaciones relacionadas con su reacción.[28] Desde entonces, sin embargo, han sido las reacciones catalizadas por Pd las más utilizadas para la formación de enlaces alquilo–arilo usando haluros o pseudohaluros de arilo. De esta forma, sólo unos pocos ejemplos de esta reacción catalizada por Ni se han publicado hasta la fecha, a pesar de que la alternativa para la formación de este enlace, consistente en el uso de electrófilos de alquilo y reactivos de arilzinc, se desaconsejaba habitualmente debido a la posible β-eliminación de hidrógeno en el complejo metálico intermedio.[22]

Algunas de las aportaciones más notables en este capítulo se han debido a Knochel[29,30] y Huo.[31] También se ha utilizado Ni/C como catalizador heterogéneo para el acoplamiento cruzado de reactivos de zinc funcionalizados y cloruros de arilo sustituidos.[32] Otras aportaciones han permitido la formación del haluro de alquilzinc *in situ* y su acoplamiento a cloropirazinas en un procedimiento que transcurre en una única operación sintética.[33]

Teniendo en cuenta estos precedentes, comenzamos nuestro estudio ensayando la reacción entre *p*-yodoanisol (**1a**) y el bromuro de alquilzinc **2a** como modelo para la optimización del sistema catalítico (**Esquema III**). El complejo estable a la humedad y al aire $[Ni(py)_4Cl_2]$[34] condujo a los mejores resultados en presencia de bipiridina.[35]

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[28] Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823.

[22] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

[29] Jensen, A. E.; Dohle,W.; Knochel, P. *Tetrahedron* **2000**, *56*, 4197-4201.

[30] Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529-5532.

[31] Huo, S. *Org. Lett.* **2003**, *5*, 423-425

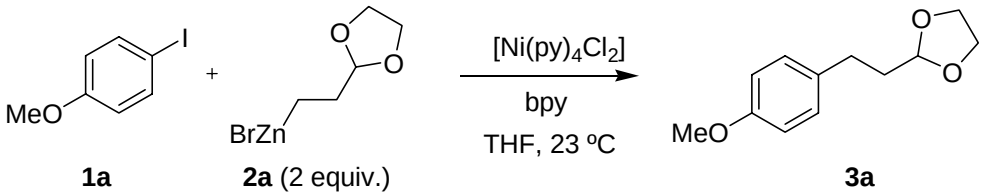
[32] Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819-5820.

[33] Walters, I. A. S. *Tetrahedron Lett.* **2006**, *47*, 341-344.

[34] (a) Long, G. J.; Clarke, P. J. *Inorg. Chem.* **1978**, *17*, 1394-1401. (b) Bachman, R. E.; Whitmire, K. H.; Mandal, S.; Bharadwaj, P. K. *Acta. Crystallogr. Sect. C* **1992**, *48*, 1836-1837.

[35] 2,2'-Bipyridine; Commercially available, Sigma-Aldrich (D216305).

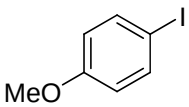
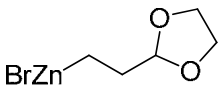
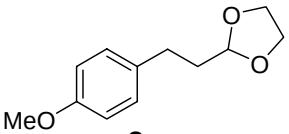
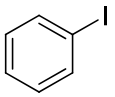
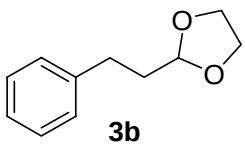
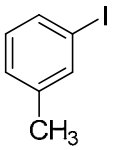
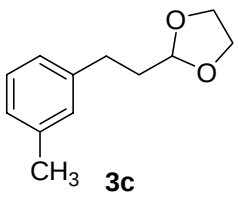
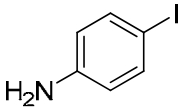
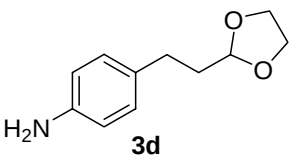
Además hay que subrayar que la reacción procedía con tan solo un 3% de carga de catalizador, completándose con la misma eficiencia y transcurriendo con un aumento poco significativo del tiempo de reacción comparado con los ensayos realizados utilizando un 10% de catalizador.

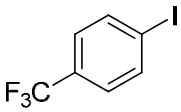
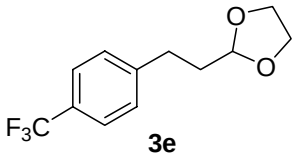
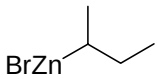
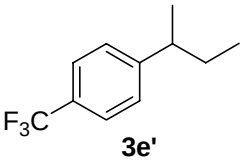


Esquema III

Los resultados de la siguiente tabla (**Tabla 1**) dejaban constancia de que la reacción era general y toleraba la presencia de diferentes grupos funcionales.

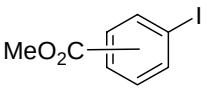
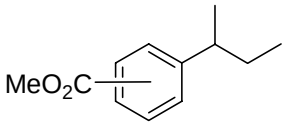
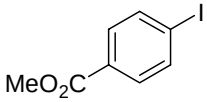
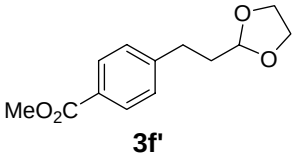
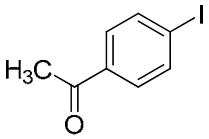
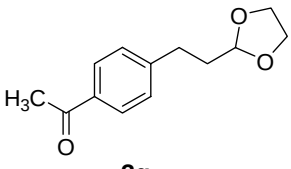
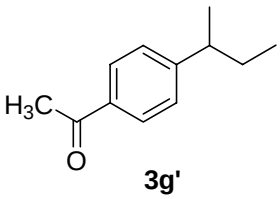
Tabla 1. *Reacciones de acoplamiento cruzado catalizadas por Ni de yoduros de arilo con bromuros de alquilzinc.*

Entrada	ArI	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **1a**	 **2a**	 **3a**	3.5	80
2	 **1b**		 **3b**	9	78
3	 **1c**	**2a**	 **3c**	6	60
4	 **1d**		 **3d**	42	46

5	 **1e**		 **3e**	8	69
6		 **2b**	 **3e'**	3	58

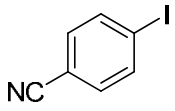
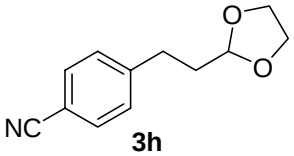
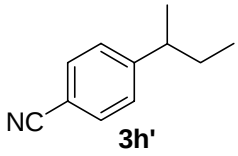
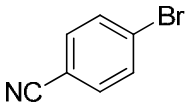
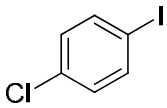
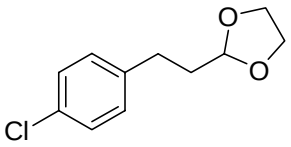
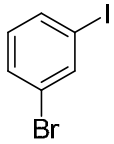
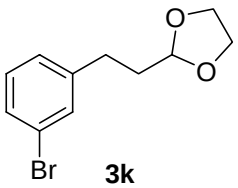
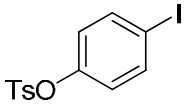
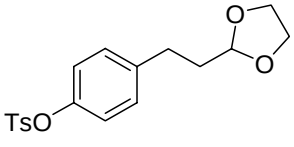
Una gran variedad de grupos funcionales con carácter atractor de electrones resultaban también compatibles con la formación de los productos de acoplamiento cruzado (**Tabla 2**).

Tabla 2. *Reacciones de acoplamiento cruzado catalizadas por Ni de yoduros de arilo que contienen grupos atractores de electrones con bromuros de alquilzinc.*

Entrada	ArI	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **1f-*o*** (*orto*)	**2b**	 **3f-*o*** (*ortho*)	2	43
2	**1f-*m*** (*meta*)		**3f-*m*** (*meta*)	2	56
3	**1f-*p*** (*para*)		**3f-*p*** (*para*)	2	60
4	 **1f-*p***	**2a**	 **3f'**	12	75
5	 **1g**	**2a**	 **3g**	3	66
6		**2b**	 **3g'**	3	84

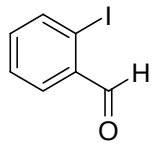
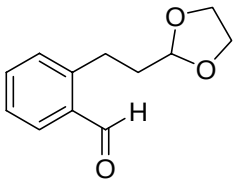
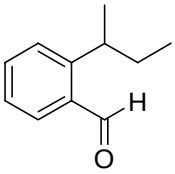
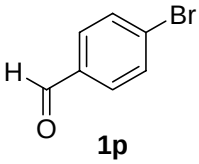
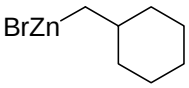
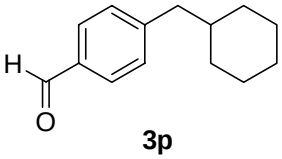
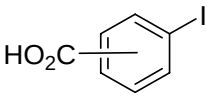
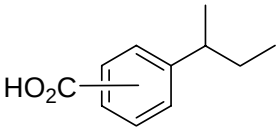
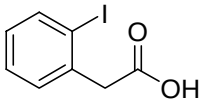
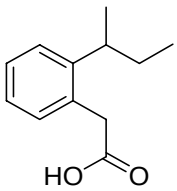
Bajo estas condiciones, los bromuros de arilo mostraron una reactividad menor. Sin embargo el *p*-bromobenzonitrilo (**1i**), que contiene un grupo atractor de electrones, condujo con éxito al producto de acoplamiento (entrada 3, **Tabla 3**). El clorobenceno, el bromobenceno y el *p*-bromoanisol permanecieron inalterados bajo las condiciones de reacción estándar. Los compuestos que contenían Cl, Br o tosilato en el anillo aromático reaccionaban quimioselectivamente a través del enlace C–I (**Tabla 3**).

Tabla 3*. Reacciones quimioselectivas de acoplamiento cruzado catalizadas por Ni de yoduros de arilo y del* p*-bromobenzonitrilo con broumuros de alquilzinc***.**

Entrada	ArI	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **1h**	**2a**	 **3h**	3	83
2	**1h**	**2b**	 **3h'**	3	65
3	 **1i**	**2b**	**3h'**	3	65
4	 **1j**	**2a**	 **3j**	2.5	75
5	 **1k**		 **3k**	2	75
6	 **1l**		 **3l**	9	65

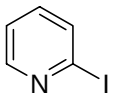
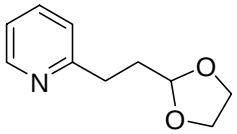
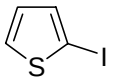
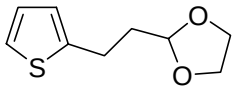
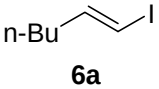
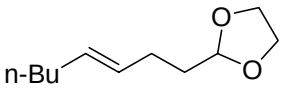
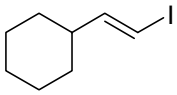
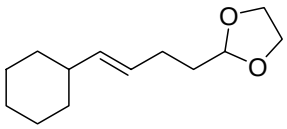
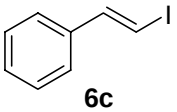
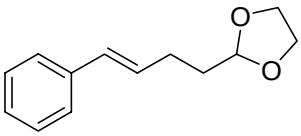
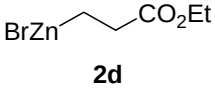
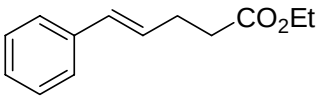
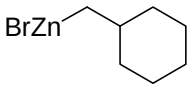
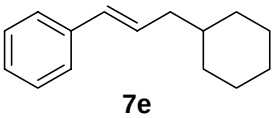
También se acoplaron, con rendimientos moderados o buenos, los aldehídos y los ácidos carboxílicos, que contienen hidrógenos ácidos (**Tabla 4**).

Tabla 4. *Reacciones de acoplamiento cruzado catalizadas por Ni de yoduros de arilo que contienen aldehídos o ácidos carboxílicos con bromuros de alquilzinc.*

Entrada	ArI	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **1o**	**2a**	 **3o**	8	52
2		**2b**	 **3o'**	3	70
3	 **1p**	 **2c**	 **3p**	4	83
4	 **1q-*o*** (*ortho)*	**2b**	 **3q-*o*** (*ortho*)	1.5	89
5	**1q-*m*** (*meta*)		**3q-*m*** (*meta*)	1.5	50
6	**1q-*p*** (*para*)		**3q-*p*** (*para*)	1.5	56
7	 **1r**	**2b**	 **3r**	2	77

También se acoplaron yoduros heteroaromáticos y de alquenilo (**Tabla 5**).

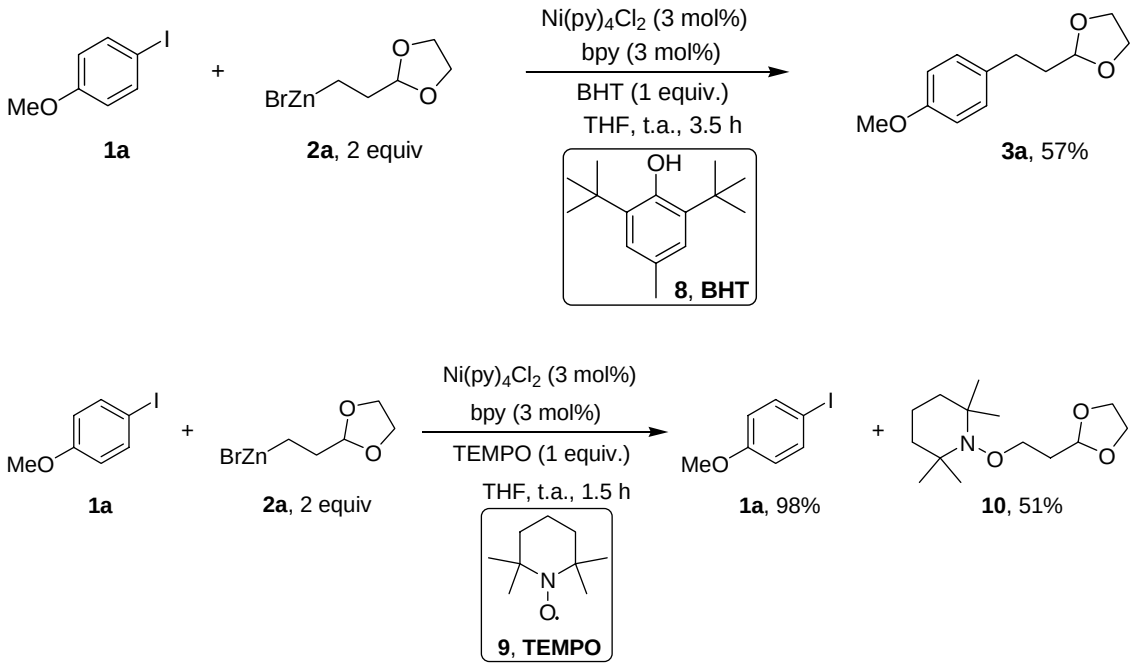
***Tabla 5**. Reacciones de acoplamiento cruzado catalizadas por Ni de yoduros de heteroarilo y alquenilo con bromuros de alquilzinc.*

Entrada	R-I	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **4a**	**2a**	 **5a**	14	64
2	 **4b**	**2a**	 **5b**	12	65
3	 **6a**	**2a**	 **7a**	7	61
4	 **6b**	**2a**	 **7b**	1	71
5	 **6c**	**2a**	 **7c**	2	71
6	**6c**	 **2d**	 **7d**	11	51
7	**6c**	 **2c**	 **7e**	1	87

Sin embargo, el *p*-nitroyodobenceno no condujo al producto de acoplamiento, lo que sugería que la reacción podría transcurrir por un mecanismo radicálico.

Con el fin de confirmar esta hipótesis, la reacción se llevó a cabo en presencia de inhibidores radicálicos (**Esquema IV**). Cuando se ensayó en presencia de 1 equivalente de BHT el rendimiento de la reacción sólo disminuyó ligeramente (61%), lo que indicaba la ausencia de radicales carbonados. En su lugar, el proceso se inhibía

eficazmente mediante la adición de TEMPO, que se acoplaba con el fragmento alquilo probablemente por reacción del reactivo de organozinc con un intermedio alquil-Ni(I).[36]



Esquema IV

Con el fin de averiguar más detalles sobre el transcurso de esta reacción se llevó a cabo un estudio computacional que arrojó resultados interesantes sobre el mecanismo.

De acuerdo con los precedentes bibliográficos[37,38,39,40,41] y una vez descartadas algunas de las propuestas mecanísticas anteriormente sugeridas por otros autores, mediante los análisis computacionales pertinentes, el estudio se restringió a dos posibles alternativas que implicaban ciclos catalíticos donde intervenían especies Ni^{I}-Ni^{III} y donde los derivados radicálicos de Ni^{I} se proponían como los verdaderos catalizadores de la reacción (**Esquema V**). En el primer ciclo (**Esquema V**, (*a*)) tendría lugar una transmetalación sobre Ni^{I} previa a la adición oxidante del haluro de arilo. En el segundo ciclo (**Esquema V**, (*b*)), se produciría la adición oxidante del haloareno sobre el

[36] Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.

[37] Kochi, J. *Pure Appl. Chem.* **1980**, *52*, 571-605.

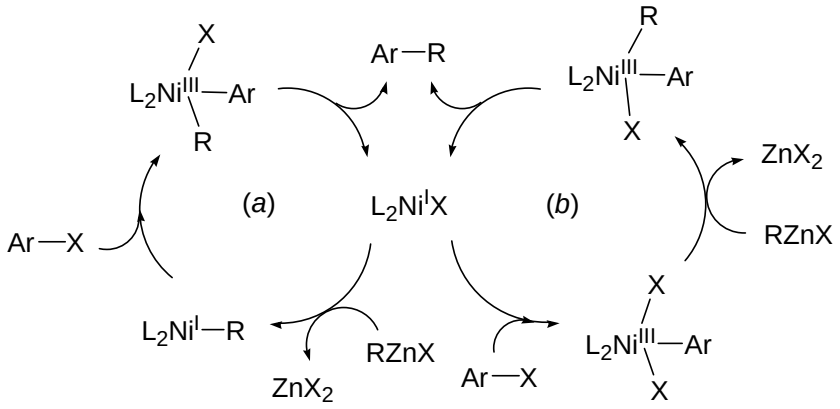
[38] Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *72*, 7262-7270.

[39] Klein, A.; Budnikova, Y. H.; Sinyashin, O. G. *J. Organomet. Chem.* **2007**, *692*, 3156-3166.

[40] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680-3688.

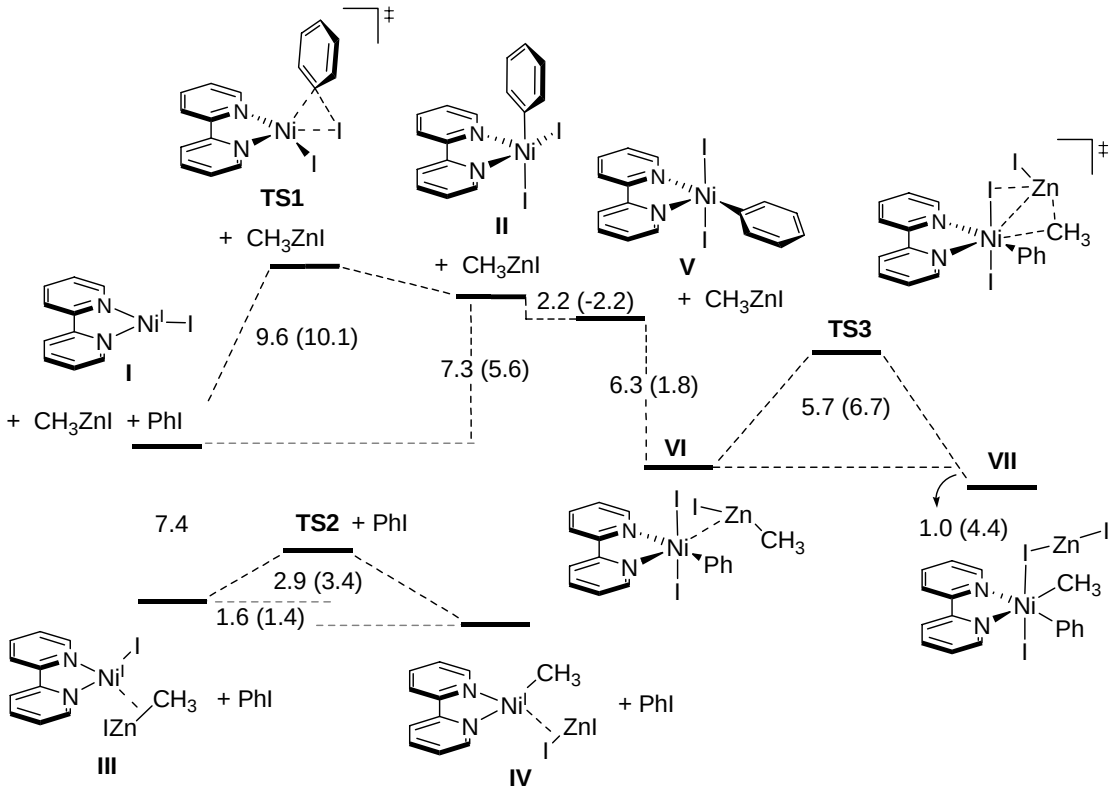
[41] (a) Jones, G. D.; Mcfarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Comm.* **2005**, 4211-4213. (b) Anderson, T. J.; Vicic, D. A. *Organometallics* **2004**, *23*, 623-625.

catalizador activo y el complejo de Ni^{III} resultante reaccionaría con el haluro de alquilzinc.



Esquema V

Como modelo para realizar el estudio computacional se seleccionó Ni(bpy)I (**I**, **Esquema VI**). Los perfiles calculados para el transcurso de la reacción de **I** con PhI y MeZnI a través de la adición oxidante y la transmetalación, respectivamente, se muestran en el **Esquema VI**.



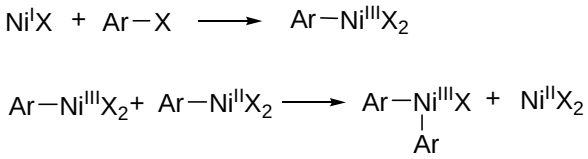
Las energías de reacción y de activación (Δ(E+ZPE) kcal mol^{-1}) fueron calculadas a nivel B3LYP/6-31G(C, N, H), LANL2DZ (Zn, Ni, I). Los valores mostrados entre paréntesis corresponden a las energías expresadas en kcal mol^{-1} y calculadas en THF con el modelo PCM.*

Esquema VI

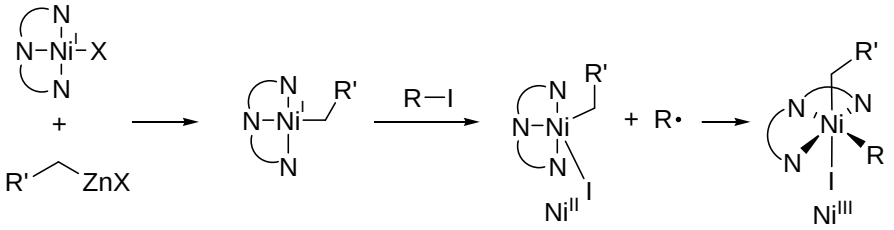
En definitiva, nuestros resultados sugerían que el ciclo catalítico real implicaba una transmetalación inicial del intermedio de Ni^{I} con el haluro de arilo dando lugar a la formación de un intermedio diorgano-Ni^{III}, tal como se muestra en el **Esquema V**, (*a*).

Es importante subrayar que aunque los ciclos catalíticos de Ni^{I}-Ni^{III} parecen operar en otras reacciones de acoplamiento cruzado catalizadas por Ni, el papel de los diferentes estados de oxidación y la activación del electrófilo no son los mismos que en el caso que nos ocupa (ver **Esquema VII**).[42,43,44]

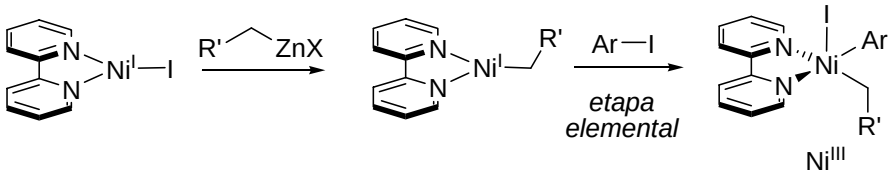
a) Homoacoplamiento of haloarenos



b) Acoplamiento cruzado de Negishi alquilo-alquilo



c) Acoplamiento cruzado de Negishi alquilo-arilo



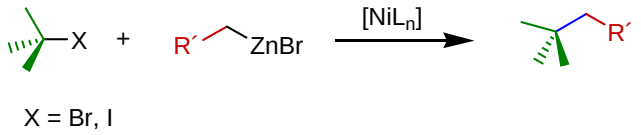
Esquema VII

[42] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100-8101.

[43] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

[44] Chass, G. A.; O'Brien, C. J.; Hadei, N.; Kantchev, E. A. B.; Mu, W. -H.; Fang, D. -C.; Hopkinson, A. C.; Csizmadia, I. G.; Organ, M. G. *Chem. Eur. J.* **2009**, *15*, 4281-4288.

También se ensayaron reacciones de acoplamiento cruzado de haluros de alquilo y haluros de alquilzinc y alquilmagnesio catalizadas por Ni para la *formación de enlaces* $C(sp^3)$–$C(sp^3)$ (**Esquema VIII**).



Esquema VIII

Como se ha mencionado previamente, durante muchos años los acoplamientos cruzados de electrófilos alquílicos parecían desfavorables debido a la dificultad de la adición oxidante y la posibilidad de la *β*-eliminación de hidrógeno durante el curso de la reacción. Recientemente, sin embargo, algunos estudios han demostrado claramente que estos problemas pueden de hecho solventarse.

Entre los estudios más destacables sobre la reacción de acoplamiento cruzado catalizada por Ni para la formación de enlaces alquilo–alquilo utilizando reactivos de alquilzinc se encuentran los trabajos de Knochel y colaboradores.[45,46,47,48,49] En 2003, Fu publicó que el sistema catalítico $Ni(cod)_2$ (cod: (*Z*,*Z*)-1,5-ciclooctadieno)/(4%)/(*sec*-Bu)-pybox (8%), en DMA (*N*,*N*-dimetilacetamida) catalizaba el acoplamiento cruzado de una variedad de bromuros de alquilo primarios y secundarios con haluros de alquilzinc.[50] Posteriormente consiguió extender significativamente la aplicación de este método,[51] publicando acoplamientos cruzados que, incluso, transcurrían con inducción asimétrica.[52,53,54] Resultaba especialmente interesante el hecho de que el acoplamiento

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45 Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1996**, *34*, 2723-2725.

46 Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544-3553.

47 Giovannini, R.; Stüdemnann, N.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390.

48 Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323-1326.

49 Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79-85.

50 Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

51 (a) Smith S. W.; Fu, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 9334-9336. (b) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211-4213.

52 Fisher, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595.

53 Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483.

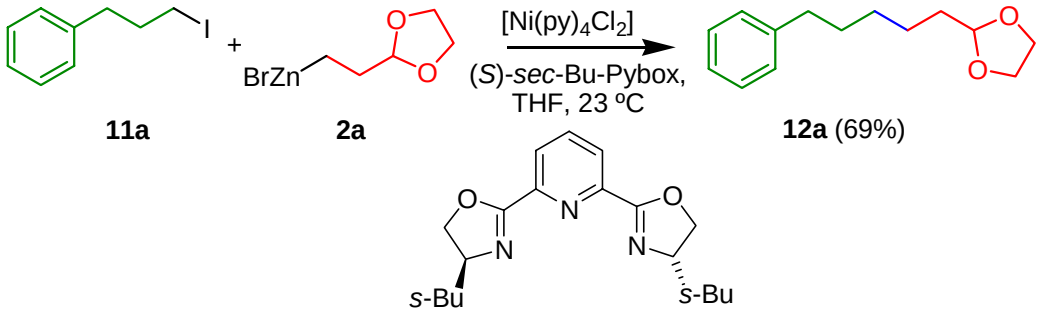
54 Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756-2757.

de Negishi de haluros de alquilo con nucleófilos de alquilzinc parecía seguir un mecanismo diferente aunque todavía no bien entendido.[55]

Por otro lado, Kambe y colaboradores encontraron que el acoplamiento cruzado de cloruros, bromuros y tosilatos de alquilo, con reactivos de Grignard o con reactios de organozinc, podía ser catalizado de manera eficiente por Ni bajo unas condiciones de reacción específicas que incluían el empleo de dienos como aditivos y donde se proponían ciclos catalíticos en los que intervenían especies de Ni(II) y Ni(IV).[56,57,58]

Considerando estos precedentes y con el fin de optimizar un proceso efectivo de acoplamiento de haloalcanos con haluros de alquilzinc y alquilmagnesio, se ensayaron diversas reacciones de acoplamiento que permitieron, además, profundizar en el conocimiento del mecanismo de la reacción.

Inicialmente se estudió la reacción del haluro de alquilo primario **11a** con un bromuro de alquilzinc (**Esquema IX**). Se consideró entonces detenidamente el precedente de Fu y se decidió sustituir el complejo sensible al aire usado por este autor, $Ni(cod)_2$, por el más estable y fácilmente manipulable $Ni(py)_4Cl_2$. Este catalizador junto con el ligando (*S*)-(*sec*-Bu)-pybox, resultó ser la combinación más favorable para el acoplamiento alquilo–alquilo de **11a** con el bromuro de alquilzinc **2a** que transcurrió con buen rendimiento (69%).



Esquema IX

[55] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100-8101.

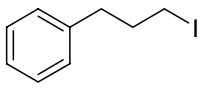
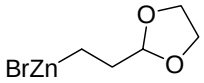
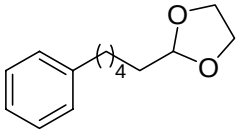
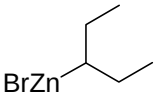
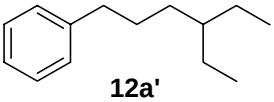
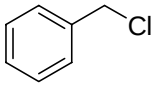
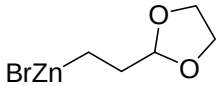
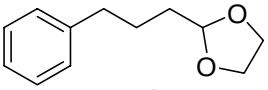
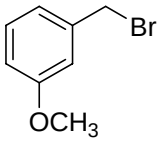
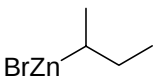
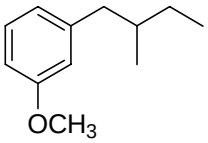
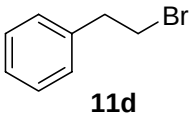
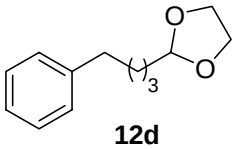
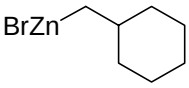
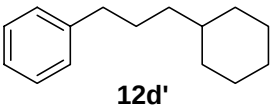
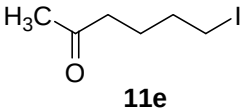
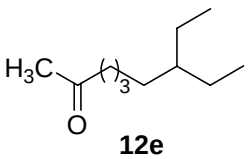
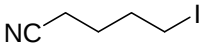
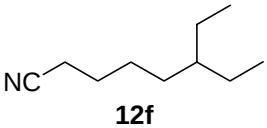
[56] Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223.

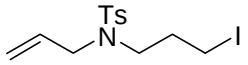
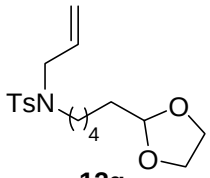
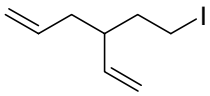
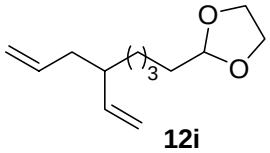
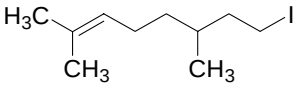
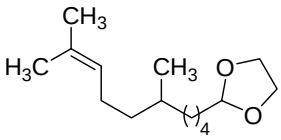
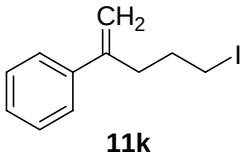
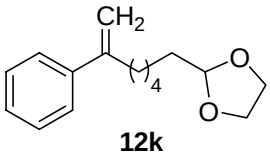
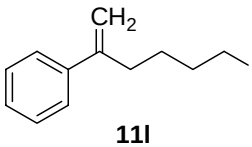
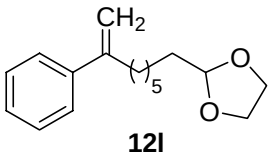
[57] Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646-5647.

[58] Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 6180-6182.

Igualmente, diversos bromuros y yoduros de alquilo condujeron a los productos de acoplamiento, incluso frente a reactivos de alquilzinc secundarios (**Tabla 6**). Los cloroalcanos y los bromuros terciarios no reaccionaron bajo estas condiciones, sin embargo, la reacción con los yoduros se mostró compatible con grupos funcionales tales como cetona, ciano o tosilamidas (entradas 7, 8 y 9, **Tabla 6**).

Tabla 6. *Reacciones de acoplamiento cruzado catalizadas por Ni de haloalcanos primarios con bromuros de alquilzinc.*[a]

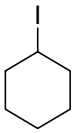
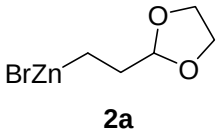
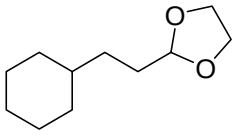
Entrada	Sustrato	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **11a**	 2a	 **12a**	11	69
2	**11a**	 **2e**	 **12a'**	18	61
3	 **11b**	 **2a**	 **12b**	2	71
4	 **11c**	 **2b**	 **12c**	1	63
5	 **11d**	**2a**	 **12d**	11	73
6	**11d**	 **2c**	 **12d'**	8	62
7	 **11e**	**2e**	 **12e**	11	66
8	 **11f**	**2e**	 **12f**	11	71

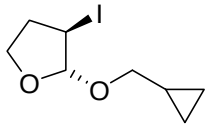
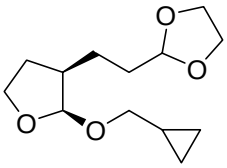
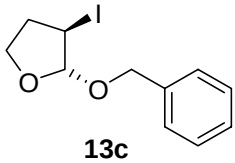
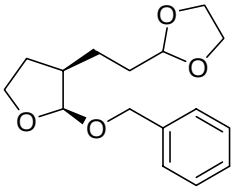
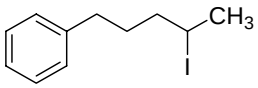
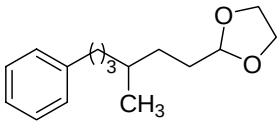
9	 **11g**	**2a**	 **12g**	18	63
11	 **11i**	**2a**	 **12i**	5	66
12	 **11j**	**2a**	 **12j**	8	76
13	 **11k**	**2a**	 **12k**	9	82
14	 **11l**	**2a**	 **12l**	11	69

[a]Condiciones: $[Ni(py)_4Cl_2]$ (10 mol %), (*S*)-(*sec*-Bu)-pybox (10 mol %), 4 equiv RZnBr en THF a 23 ºC.

Además se pudo comprobar que la reacción también tenía lugar entre yoduros de alquilo secundarios y bromuros de alquilzinc primarios (**Tabla 7**).

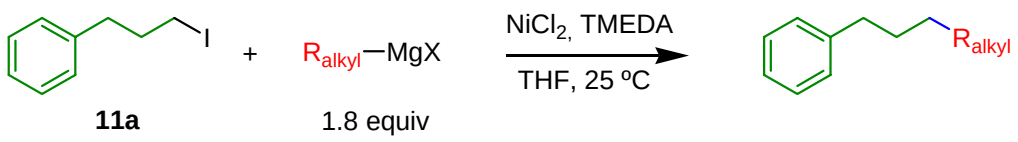
Tabla 7. *Reacciones de acoplamiento cruzado catalizadas por Ni de yodoalcanos secundarios con bromuros de alquilzinc.*[a]

Entrada	Sustrato	RZnBr	Producto	t (h.)	Rdto. (%)
1[b]	 **13a**	 **2a**	 **14a**	11	74

2[c]	 **13b**	**2a**	 **14b**	6	79
3[c]	 **13c**	**2a**	 **14c**	16	72
4	 **13d**	**2a**	 **14d**	3	73

[a]Condiciones: $[Ni(py)_4Cl_2]$ (10 mol %), (*S*)-(*sec*-Bu)-pybox (10 mol%), 4 equiv. RZnBr en THF a 23 ºC. [b]Si se usa tpy como ligando el rendimiento aislado es 51%. [c]La estereoquímica relativa mostrada es la más probable para el isómeros mayoritario, pero es tentativa. Los datos de NOE son consistentes con la configuración relativa, pero el solapamiento de las señales en el espectro de ^{1}H NMR impide la confirmación.

Dado que el acoplamiento cruzado de yodoalcanos con haluros de alquilmagnesio catalizado por Ni podría también conducir a la formación de enlaces $C(sp^3)$–$C(sp^3)$, se trabajó en la optimización de las condiciones para conseguir que dicho proceso transcurriera de forma eficaz. En el caso de emplear yoduros primarios los mejores resultados se obtuvieron usando $NiCl_2$ (5%), disponible comercialmente,[59] junto con TMEDA (*N*,*N*,*N'*,*N'*-tetrametiletilen-diamina) (10%) en THF a 25 ºC (**Esquema X**, **Tabla 8**).

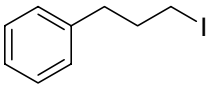
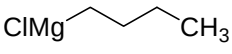
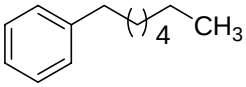
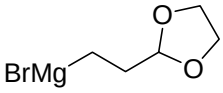
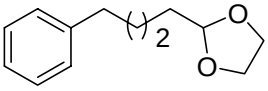
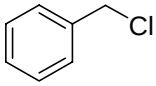
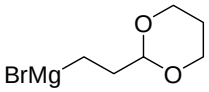
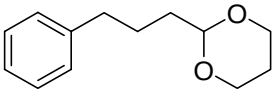
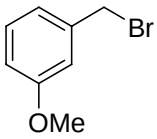
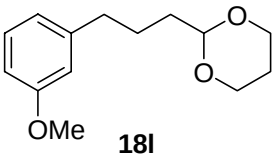
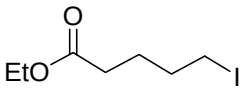
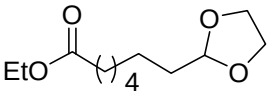


11a

Esquema X

[59] Nickel (II) chloride, anhydrous powder (99.99%): Aldrich, ref. 451193.

Tabla 8. *Acoplamiento cruzado catalizado por Ni de yodoalcanos primarios con haluros de alquilmagnesio.*

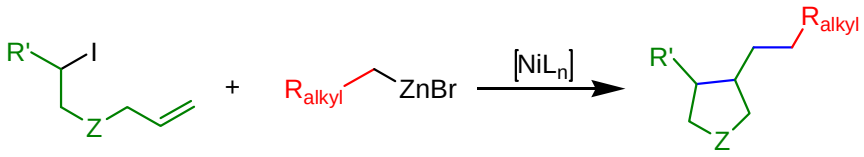
Entrada	Sustrato	RMgX	Producto	t (h.)	Rdto. (%)
1	 **11a**	 **17a**	 **18a**	2	75
2	**11a**	 **17b**	 **12a**	7	80
4	 **11k**	 **17c**	 **18k**	2	31
5	 **11l**	**17c**	 **18l**	2	41
6	 **11m**	**17c**	 **18m**	7	42

La reacción de Ueno-Stork (ciclación radicálica de alquenos que contienen haloacetales) se ha utilizado extensamente para la construcción de anillos de cinco miembros.[60] Esta reacción transcurre según un mecanismo radicálico que requiere el uso de un iniciador en cantidad estequiométrica. Considerando la hipótesis sobre la posible naturaleza radicálica de los procesos de acoplamiento de haluros de alquilo con haluros de alquilzinc catalizados por Ni, se intentó extender la reacción a un proceso en cascada de ciclación y acoplamiento que diera lugar, en una única operación sintética, a la formación de varios enlaces alquilo–alquilo.[61]

[60] (a) Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566-1577. (b) Salom-Roig, X. J.; Denes, F.; Renaud, P. *Synthesis* **2004**, 1903-1928.

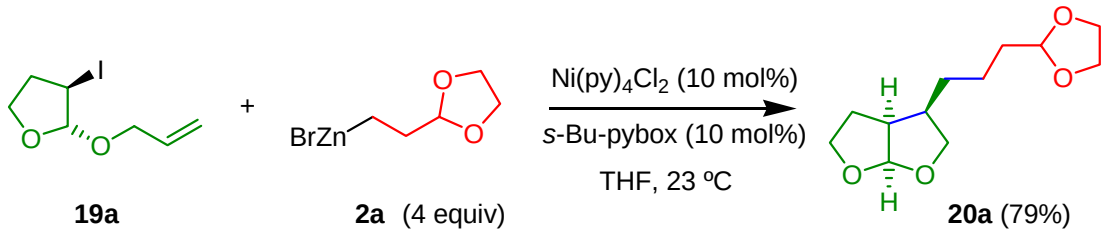
[61] Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059-6064.

Así, desarrollamos un procedimiento catalizado por Ni que permitía, de forma secuencial, la ciclación de haluros de alquilo que contienen un alqueno y el acoplamiento del radical resultante con bromuros de alquilzinc, dando lugar a la formación conjunta de dos enlaces alquilo−alquilo (**Esquema XI**).



Esquema XI

La optimización de las condiciones de reacción se llevó a cabo sobre la reacción del yodoacetal **19a** con el reactivo de organozinc comercial **2a** (4 equiv.). Los resultados más favorables se obtuvieron utilizando de nuevo el complejo estable $[Ni(py)_4Cl_2]$ junto con el ligando *sec*-Bu-pybox (**Esquema XII**), este ligando ya había sido descrito por Fu como el más efectivo en acoplamientos cruzados simples de reactivos de organozinc catalizados por Ni.[50]



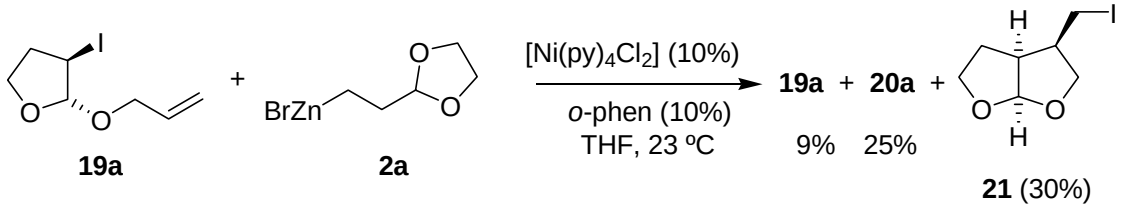
19a **2a** (4 equiv) **20a** (79%)

Esquema XII

En presencia de $Ni(py)_4Cl_2$/*o*-fenantrolina, se obtuvo además el derivado **21** con un 30% de rendimiento (**Esquema XIII**). La formación de este compuesto apoyaba un mecanismo radicálico, ya que se conocía que la reacción de **19a** con BEt_3 conducía a dicho derivado **21**, que no puede descartarse como intermedio en la formación de **20a**.[62]

[50] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

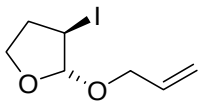
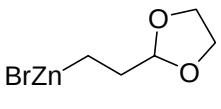
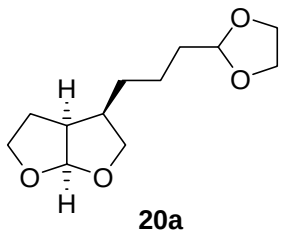
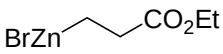
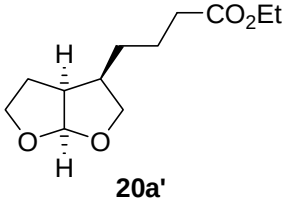
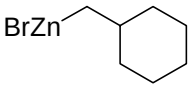
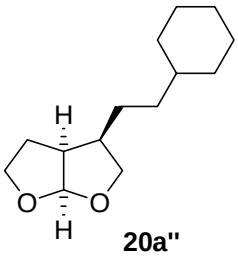
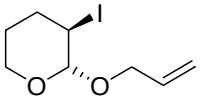
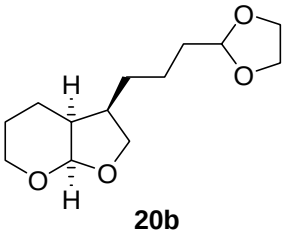
[62] (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604-8605. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041-11047.

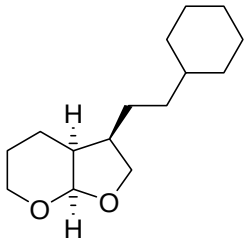
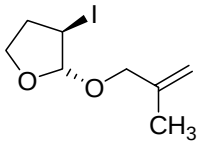
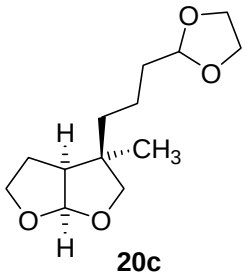
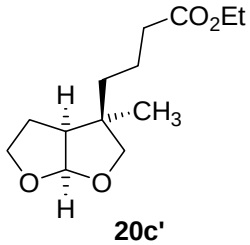
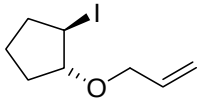
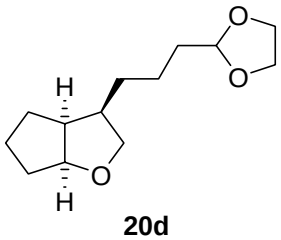
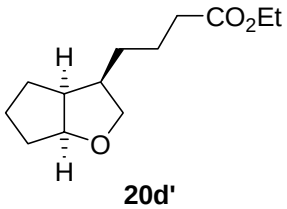
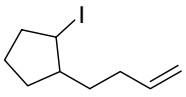
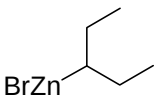
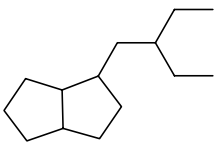


Esquema XIII

De esta forma, la reacción de ciclación/acoplamiento se mostró general y extensible a una gran variedad de sustratos mediante el empleo de $[Ni(py)_4Cl_2]$ junto con el ligando *sec*-Bu-pybox en THF a temperatura ambiente (**Tabla 9**).

Tabla 9. *Reacciones de ciclación y acoplamiento cruzado de yoduros de alquilo cíclicos, que contienen un alqueno, con bromuros de alquilzinc.*

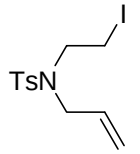
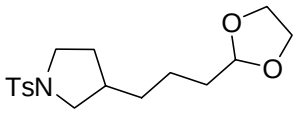
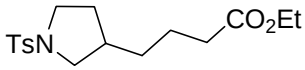
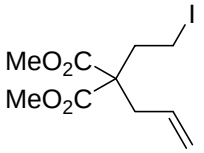
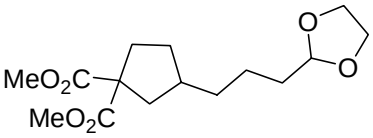
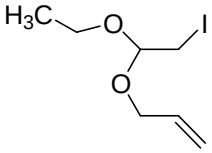
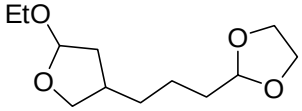
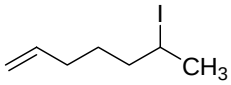
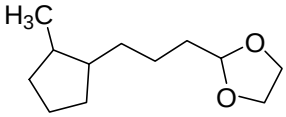
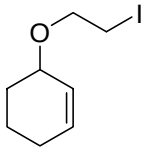
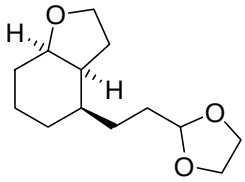
Entrada	Sustrato	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **19a**	 **2a**	 **20a**	7	79
2	**19a**	 **2d**	 **20a'**	13	65
3	**19a**	 **2c**	 **20a''**	15	60
4[a]	 **19b**	**2a**	 **20b**	8	83 (92:8)

6[a]	**19b**	**2c**	 **20b''**	8	81 (93:7)
7	 **19c**	**2a**	 **20c**	8	64
8	**19c**	**2d**	 **20c'**	15	68
9[b,c]	 **19d**	**2a**	 **20d**	9	76 (64:36)
10[b,c]	**19d**	**2d**	 **20d'**	13	81 (57:43)
11[d]	 **19e**	 **2e**	 **20e**	24	73

[a]Medido por GC-MS. El isómero minoritario muestra la configuración opuesta en C3. [b]La configuración relativa mostrada corresponde al isómero mayoritario. El minoritario es el epímero en C3. [c]Los isómeros fueron separados por cromatografía en columna. [d]Mezcla de diastereoisómeros (más de dos).

Los yodoalcanos de cadena abierta dieron lugar también a los correspondientes productos de ciclación/acoplamiento (**Tabla 10**).

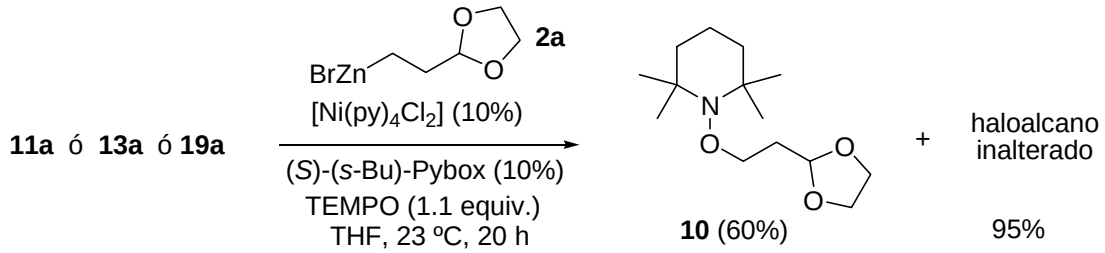
Tabla 10. *Reacción de ciclación y acoplamiento cruzado de yoduros de alquilo de cadena abierta, que contienen un alqueno, con bromuros de alquilzinc.*

Entrada	Sustrato	RZnBr	Producto	t (h.)	Rdto. (%)
1	 **23a**	**2a**	 **24a**	16	83
2	**23a**	**2d**	 **24a'**	19	66
3[a]	 **23b**	**2a**	 **24b**	7	63
4	 **23c**	**2a**	 **24c**	7	55
5[b]	 **23d**	**2a**	 **24d**	11	84
6[c]	 **23e**	**2a**	 **24e**	11	46

[a]El producto de acoplamiento sin ciclación se forma en un 13% de rendimiento (ambos compuestos no pudieron separarse. Los rendimientos se calcularon sobre el espectro ^{1}H NMR de la mezcla). [b]El producto de acoplamiento sin ciclación se forma en un 29% de rendimiento (ambos compuestos no pudieron separarse. Los rendimientos se calcularon sobre el espectro ^{1}H NMR de la mezcla). [c]El producto de acoplamiento sin ciclación se forma en un 36% de rendimiento (rendimiento del producto aislado).

Se llevaron a cabo diversos experimentos con el propósito de obtener información acerca del mecanismo por el que transcurre este proceso, entre ellos los que incluían el uso de inhibidores radicálicos. En presencia de BHT se observó una inhibición parcial del proceso en cascada para el sustrato **19a**. Por otro lado, cuando la

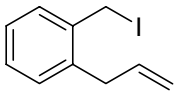
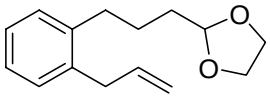
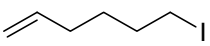
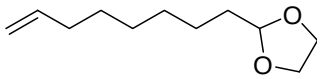
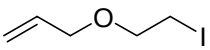
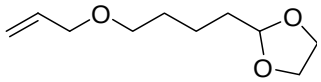
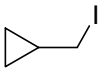
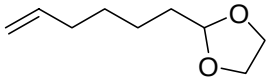
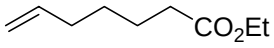
reacción se llevó a cabo en presencia del inhibidor radicálico TEMPO se obtuvo el producto de acoplamiento de éste con el radical derivado de **2a** (**Esquema XIV**).



Esquema XIV

También se decidió explorar el comportamiento de varios relojes radicálicos bajo las condiciones optimizadas para la reacción.[63] Los resultados obtenidos se recogen en la siguiente tabla (**Tabla 11**).

Tabla 11. *Acoplamientos cruzados catalizados por Ni de relojes radicálicos con bromuros de alquilzinc ([Ni(py)$_4$Cl$_2$] (10 mol %), (S)-(sec-Bu)-pybox (10 mol %), THF, 23 ºC).*

Entrada	Sustrato	RZnBr	Producto	k (s^{-1})[a]	t (h.)	Rdto. (%)
1	 **25a**	**2a**	 **26a**	0.1	3	82
2[b]	 **25b**		 **26b**	2.3×10^5	20	41
3[b]	 **25c**		 **26c**	9×10^6	11	25
4	 **25d**		 **26d**	6.7×10^7	5	63
5		**2b**	 **26d'**	6.7×10^7	4	59

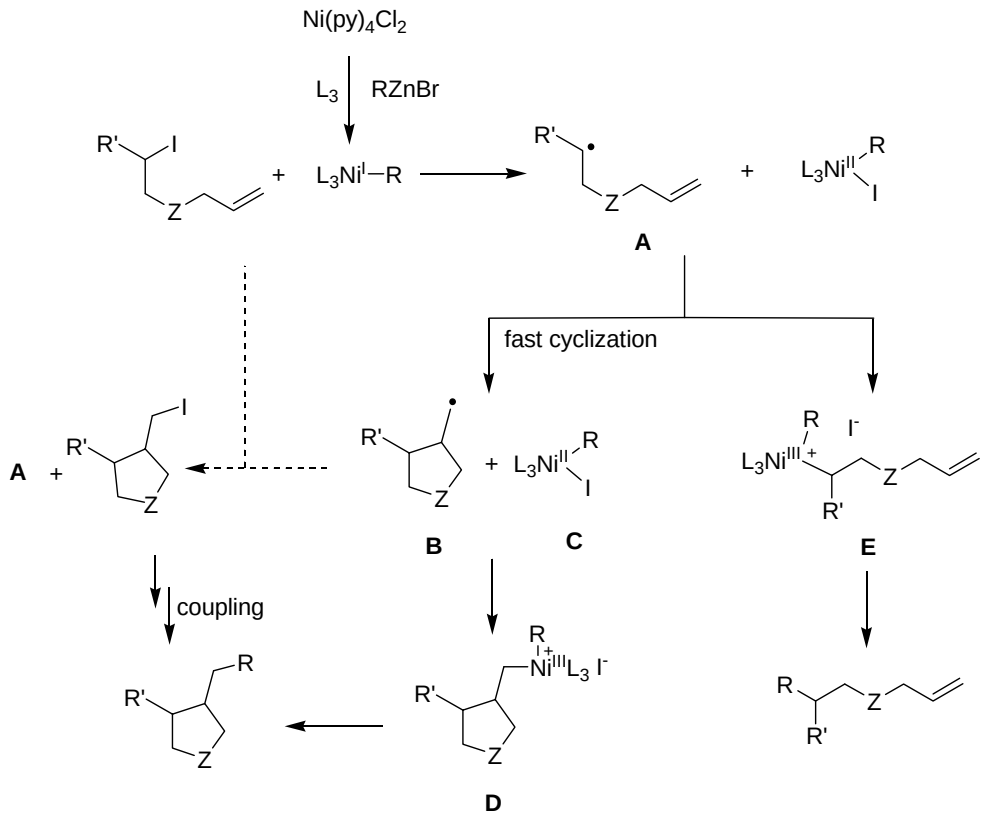
[a]Velocidad de ciclación o de apertura del radical formado desde **25a-d** después de la rotura homolítica del enlace C–I. [b]Los bajos rendimientos se deben probablemente a la formación de compuestos volátiles resultantes de la abstracción de hidrógeno del disolvente.

63 Newcomb, M., *Radicals in Organic Synthesis*, Renaud, P., Sibi, M. P., Eds., Wiley-VCH, Weinheim, **2001**, Vol. 1, capítulo 3.1, pp. 317-336.

Teniendo en cuenta la velocidad de ciclación (**Tabla 11**, entradas 1-3) o apertura de anillo (**Tabla 11**, entradas 4, and 5) para los radicales generados a partir de los correspondientes yoduros, se puede deducir que el acoplamiento C–C clave tiene lugar con una velocidad comparable a la de una reacción unimolecular, en el intervalo de 0.9 10^7-6.7 10^7 s^{-1}. Ya que lo que tiene lugar realmente es un proceso bimolecular, la reactividad intrínseca de las especies intermedias debe ser incluso mayor. De esta forma se puede concluir que la formación del enlace C–C no constituye el paso limitante de velocidad de la reacción.

Simultáneamente a Phillips y colaboradores,[64] llevamos a cabo una serie de cálculos a nivel DFT para examinar las superficies de energía potencial de las reacciones de acoplamiento cruzado alquilo–alquilo de Negishi catalizadas por Ni(I).

De acuerdo con las evidencias experimentales y los datos computacionales, el proceso parece seguir un mecanismo radicálico donde la especie Ni^I-alquilo es la principal implicada en el inicio de la reacción y puede asumirse que ésta se ajusta a un ciclo catalítico Ni^I-Ni^{III}. Un posible mecanismo de reacción podría ser el que se muestra en el siguiente esquema (**Esquema XV**).



Esquema XV

[64] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680-3688.

Hace más de medio siglo, Kharasch y colaboradores investigaron el efecto de las sales de los metales de transición tales como hierro y cobalto en reacciones entre haluros orgánicos y reactivos de Grignard.[65] La reacción resultaba virtualmente incontrolable debido a la obtención de mezclas de productos de homoacoplamiento, desproporción y acoplamiento cruzado. Posteriormente, Kochi y colaboradores describieron las reacciones de acoplamiento cruzado selectivas utilizando catalizadores de hierro y cobre.[66] Hasta hace poco no se volvió a prestar atención a los descubrimientos de Kochi. Recientemente, sin embargo, Fürstner y colaboradores han descrito el empleo de sales de hierro sin ligandos que funcionan como catalizadores en reacciones de acoplamiento cruzado de cloruros de arilo y reactivos de Grignard.[67] Nakamura y colaboradores,[68] por un lado, y Hayashi and Nagano,[69] por otro, han desarrollado reacciones de acoplamiento entre haluros de alquilo primarios y secundarios con reactivos de Grignard catalizadas por hierro.

La ya mencionada reacción de Ueno-Stork[60] y el desarrollo de otras reacciones relacionadas con ésta, tales como la ciclaciones radicálicas con reactivos de Grignard catalizadas por Co de Oshima,[70,71,72] o las ciclaciones y acoplamientos cruzados catalizados por Pd con reactivos de organozinc[73,74] nos indujeron a intentar la

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65 (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320; (b) Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 504-507; (c) Cotton, F. A. *Chem. Rev*. **1955**, *55*, 551-594.

66 (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1483-1487. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351-360.

67 Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609-612.

61 (a) Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566-1577. (b) Salom-Roig, X. J.; Denes, F.; Renaud, P. *Synthesis* **2004**, 1903-1928.

68 Nakamura, M.; Matsuo K.; Ito, K.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686-3687.

69 Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297-1299.

70 (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374-5375. (b) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137-4139. (c) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886-1889.

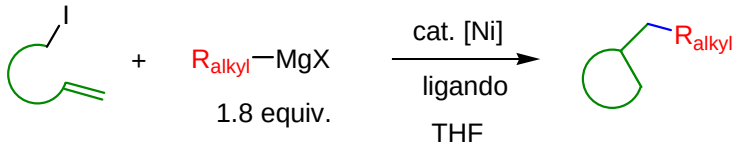
71 (a) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565-1567. (b) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 8609-8618.

72 Co-catalyzed Heck type reactions of alkyl halides: (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514-6515. (b) Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257-2259.

73 Luo, F.; Wang, R. *Tetrahedron Lett.* **1991**, *32*, 7703-7706.

74 Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323-2326.

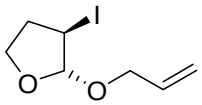
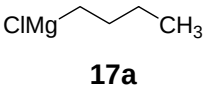
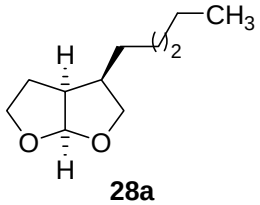
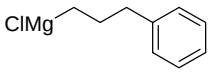
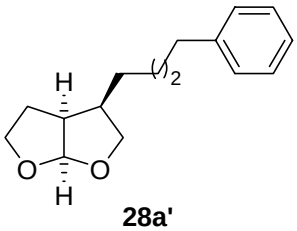
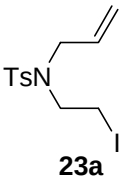
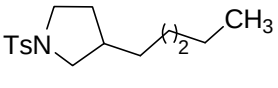
optimización de un procedimiento simple para la ciclación y acoplamiento cruzado de yodoalcanos que contuvieran un doble enlace con haluros de alquilmagnesio catalizado por Ni, un metal que, hasta donde sabemos, no había sido utilizado en catálisis para este tipo de procesos (**Esquema XVI**).

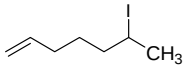
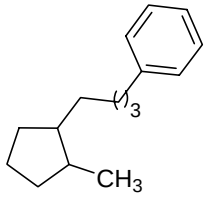
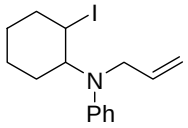
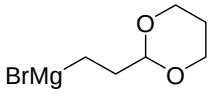
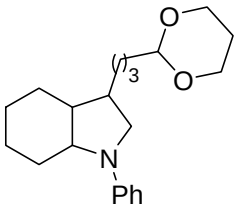
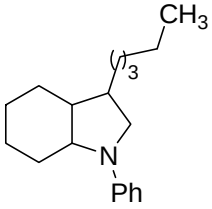


Esquema XVI

Finalmente, las condiciones de reacción anteriormente optimizadas para el acoplamiento cruzado haluros de alquilo con reactivos de alquilmagnesio resultaron, también, muy eficientes para el proceso de ciclación y acoplamiento cruzado (**Tabla 12**).

Tabla 12. *Reacción catalizada por Ni de formación de dos enlaces alquilo alquilo mediante ciclación y acoplamiento cruzado de yoduros de alquilo, que contienen un alqueno, con haluros de alquilmagnesio.*[a]

Entrada	Sustrato	R_{alkyl}–MgX	Producto	t (h.)	Yield (%)
1[b]	 **19a**	 **17a**	 **28a**	2	65
2	**19a**	 **17c**	 **28a'**	2	58
3	 **23a**	**17a**	 **29a**	1	59

4[c]	 **27b**	**17c**	 **29b**	1	54
5	 **27c**	 **17b**	 **29c**	1	61
6	**27c**	**17a**	 **29c'**	1.5	73

[a]Condiciones: $NiCl_2$ (5 mol %), TMEDA (10 mol%), 1.8 equiv. RMgX en THF a 23 ºC. [b]El bromoacetal condujo al producto deseado con un 31% de rendimiento. [c]Mezcla de dos estereoisómeros inseparables en proporción 70:30.

ABBREVIATIONS AND ACRONYMS

ABBREVIATIONS AND ACRONYMS

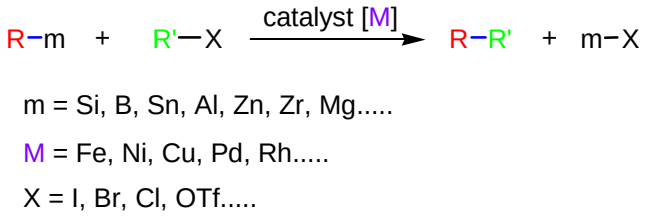
acac	acetylacetonate
Ar	aryl
BHT	Butylated hydroxytoluene (2,6-di-*tert*-butyl-4-methylphenol)
Bn	benzyl
br	broad
Cy	cyclohexyl
CH_2Cl_2	dichloromethane
DEE	diethylether
d	doublet
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
dppf	1,1'- Bis(diphenylphosphino)ferrocene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent
Et	ethyl
FAB	fast-atom bombardment
FG	functional group
GC	gas chromatography
h	hour
n-Bu	*n*-butyl
i-Pr	isopropyl
J	coupling constant (NMR)
LG	leaving group
M	molarity
m	meta
m	multiplet
Me	methyl
mol	mole
mp	melting point
MS	mass spectroscopy
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
Pent	pentyl
Ph	phenyl
q	quartet
rt	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidinyl-*N*-oxyl
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
Ts	4-toluenesulfonyl

INTRODUCTION

I. The metal-catalyzed cross-coupling reaction

Ia. Very brief history and introduction to the cross-coupling reactions

The cross-coupling reaction of organometallic reagents with organic electrophiles in the presence of group 8-10 metal catalysts, notably nickel and palladium complexes, is the method of choice for a wide range of C–C bonding processes.[1] These reactions, now accessible with a variety of organometallic reagents and electrophiles, provide a common class of synthetic transformations (**Scheme I**).



Scheme I

Due to simplicity and reliability in the C–C bond formations, as well as high efficiency of the catalytic process, the reactions have been widely employed by organic chemists in various fields. Application of the protocol ranges from syntheses of complex natural products to the preparation of biologically relevant molecules including drugs, supramolecules, and functional materials.

Presently, many organic chemists do not hesitate to use transition metal complexes for the transformation of organic molecules by forming new C–C bonds. Indeed, innumerable organic syntheses, that are not achievable by traditional synthetic methods, have been realized by the catalyzed reactions of transition metal complexes. Among these, the metal-catalyzed cross-coupling reactions have greatly contributed, without any doubt, to the development of such a new area of *''metal-catalyzed organic*

[1] (a) *Metal-catalyzed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **1998**. (b) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **2004**.

syntheses''. In 1941 the pioneering studies of Kharash and Fuchs[2] opened new synthetic avenues for Grignard reagents. The reactions of Li/Mg reagents in the presence of stoichiometric and catalytic amounts of copper halides were extensively studied for cross-coupling reactions during the 1960's and 1970's.[3] In 1971, Kochi reported the efficiency of $FeCl_3$ as a catalyst for the coupling of Grignard reagents with 1-alkenyl bromides and Li_2CuCl_4 for the $C(sp^3)-C(sp^3)$ coupling with iodoalkanes.[4]

In 1972, the nickel-catalyzed reaction of Grignard reagents with 1-alkenyl or aryl bromides and chlorides was independently reported by Kumada and Tamao[5] as well as Corriu and Masse.[6] An efficient cross-coupling reaction at $C(sp^2)$ with alkyl or aryl Grignard reagents was achieved in the presence of nickel-phosphine complex.[5a] The mechanistic study by Yamamoto also considerably contributed to the design of this powerful catalytic process.[7] In summary, there were many independent contributions to the historical evolution of cross-coupling methodology as is the common situation for other important discoveries.

In this way the reaction of Mg/Li reagents was widely studied in earlier examples, nevertheless the use of such highly reactive reagents was unfortunately complicated and limited by a lack of functional group compatibility or by competitive halogen-metal exchange leading to homocoupling products. However, although the nickel-catalyzed reactions suffered from stereochemical scrambling of the starting alkenyl halides, an effective palladium-catalyzed cross-coupling could be developed by Murahashi in the reaction of vinyl halides with aryllithiums.[8] So at that moment, palladium catalysts and less reactive organometallic reagents looked to be a more attractive combination.

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2 (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320; (b) Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 504-507; (c) Cotton, F. A. *Chem. Rev.* **1955**, *55*, 551-594.

3 *Organometallics in Organic Synthesis*, Lipshutz, B. H., Wiley, New York, 1994, pp 283-382.

4 (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1483-1487. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351-360.

5 (a) Tamao, K; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. (b) Tamao, K; Zembayashi, M.; Kiso, Y.; Kumada, M. *J. Organomet. Chem.* **1973**, *55*, C91-94. (c) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180-186.

6 Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, *3*, 144-145.

7 Yamamoto, A. *J. Organomet. Chem.* **2000**, *600*, 159-167.

8 Yamamura, M.; Moritani, I.; Murahashi, S. *J. Organomet. Chem.* **1975**, *91*, C39-42.

The efficiency of palladium-catalyzed processes was further demonstrated by Negishi[9] in the reactions of vinyl and aryl halides with 1-alkenyl-aluminium,[10] zinc,[11] and zirconium reagents[12]. In addition, the reaction between 1-alkenyl halides and 1-alkenyl copper(I) was reported by Normant.[13] Organostannanes were first used by Migita and Kosugi,[14] and extensive subsequent works by Stille positioned these as a mainstay of modern synthetic chemistry.[15] Suzuki and Miyaura found that organoboron compounds smoothly undergo cross-coupling reaction in the presence of a base that has been widely embraced by synthetic chemists.[16] The discovery that organopentafluorosilicates could participate in cross-coupling process by Tamao and Kumada[17] was greatly improved by Hiyama and Hatanaka to a practical C–C bond forming reaction using organosilicon compounds.[18]

Moreover, palladium-catalyzed $C(sp^2)-C(sp)$ coupling reaction between aryl or alkenyl halides or triflates and terminal alkynes, with or without the presence of a copper(I) cocatalyst, became the most important method to prepare arylalkynes and conjugated enynes (**Scheme II**). This method appeared to have a significant advantage in avoiding the preparation of organometallic reagents.

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9 Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348.

10 Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731.

11 (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823. (b) King, A. O.; Negishi, E. *J. Org. Chem.* **1978**, *43*, 358-360.

12 (a) Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168-3170. (b) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *109*, 2252-2254.

13 Alexakis, N. J. A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 959-962.

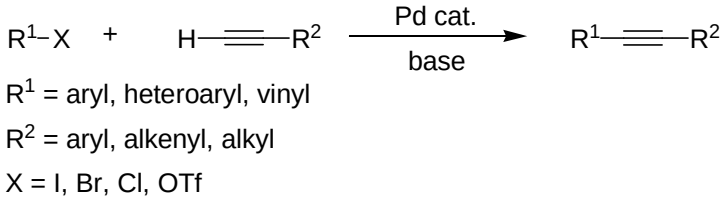
14 Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* **1983**, 839-840.

15 (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992-4998. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486.

16 Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *111*, 314-321.

17 Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics*, **1982**, *1*, 542-549.

18 (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268-270. (b) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793-7794.



Scheme II

Developments made by three seperate groups in 1975 demonstrated the importance of the protocol. In 1975, Cassar[19] and Heck[20] reported a palladium-catalyzed cross-coupling reaction of acetylides, generated *in situ* from terminal alkynes and NaOMe or triethylamine, with aryl halides. In the same year, it was found that the use of copper co-catalyst exhibits a significant accelerating effect in the presence of triethylamine.[21] The procedure, called the Sonogashira or Sonogashira-Hagihara reaction, is now accepted as the most practical method for alkynylation of aryl and 1-alkenyl halides.

Other coupling reactions of acidic C–H bonds for the formation of C−C bonds, for example allylation of enolate anions (Tsuji-Trost reaction)[22] and arylation or alkenylation of ketone enolates,[23] also have been studied extensively. More recently, the protocol was further extended to the direct coupling reaction of aromatic C–H bonds.[24]

After all those discoveries, many transition metal complexes and organometallic reagents have proven to be highly useful as catalysts and nucleophiles, respectively. Cross-coupling procedures, which utilize such coupling partners with highly covalent C–metal bonds, have found many applications in the syntheses of natural products and fine chemicals. This is due to a large extent to the simplicity of their synthesis, isolation and handling, as well as their compatibility with a wide range of functional groups. Additional attributes include safety and applicability in industrial applications. In spite

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19 Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253-259.

20 Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259-259.

21 (a) Sonogashira, K.; Tohda, Y.; Hagihara; N. *Tetrahedron Lett* **1975**, *16*, 4467-4470. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis*, **1980**, 627-630.

22 Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-395.

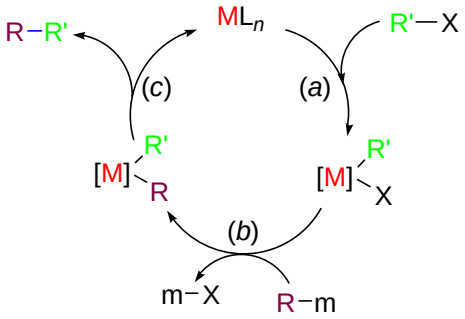
23 (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nombra, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1740-1742. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066. (c) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382-12383.

24 Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698-1712.

of the extensive use of these reactions, other analogous procedures, which can overcome the limitations of the well known processes, will be undoubtedly discovered in the future.

Ib. General mechanistic aspects of the metal-catalyzed cross-coupling reaction

The transition metal-catalyzed cross-coupling reaction, occurs by sequencial steps including an oxidative addition of the organic electrophile to a coordinatively unsaturated metal complex, followed by transmetalation from the nucleophile to the intermediate species formed in the first step, to give a diorganometal derivative, and a fast C–C reductive elimination that yields the coupled product usually regenerating the active catalyst (**Scheme III**).[1,25]



a. Oxidative addition of organic halide to a metal catalyst
b. Transmetalation from the nucleophile
c. Reductive elimination

Scheme III

A combination of the three processes has provided a very powerful and general catalytic method for C–C bond formation. All these steps are well-known processes in

[1] (a) *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **1998**. (b) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **2004**.

[25] (a) Cárdenas, D. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3018-3020. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852-860.

homogeneous catalysis,[26] although the transmetalation is less understood than the other two steps since it is highly dependent on the nature of the organometallic reagents and the reaction conditions.

Group 10 transition metals, particularly nickel and palladium, are highly effective in catalyzing cross-coupling reactions; however other metals, undergoing a simultaneous two-electron change via an oxidative addition-reductive elimination couple, can participate in similar catalytic cycles.

A variety of organometallic reagents and organic electrophiles, including those containing alkyl, aryl, alkenyl and alkynyl groups, can be also employed to assemble C–C bonds.

However, there are still limitations in the possible combination of electrophilic and nucleophilic coupling partners.[27] The comparative lack of success in cross-coupling alkyl electrophiles is often attributed to various problematic steps in the general catalytic cycle proposed for these reactions (**Scheme IV**). Particularly in the case of Pd(0) complexes, all the alkyl halides (even CH_3I) react slowly. In fact, the reactivity is believed to be generally slower than the addition of any allyl, benzyl, alkenyl or aryl electrophile.[28] Comparatively, the reaction of CH_3I with phosphane-Ni(0) complexes is much faster (about 10^7 times) than the addition of CH_3I to Pd(0) complexes, and follows a complex pathway in which radical species may be involved.[29] Once the alkyl-Pd(II) complex has been formed, there should exist the possibility of decomposition by a fast *β*-elimination of hydrogen, which competes with the usually slower transmetalation. *β*-elimination requires several conditions such as the existence of a vacant coordination site and the feasibility of arranging the M–C–C–H atoms in the same plane. This undesirable process may not be a problem in carbonylative couplings of $C(sp^3)$ centers since the fast CO insertion prevents decomposition of the alkyl-Pd intermediate.[30]

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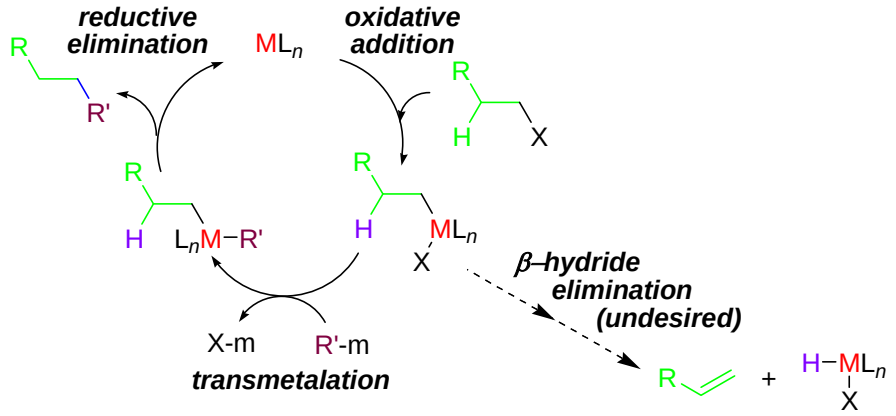
[26] *Palladium Reagents in Organic Syntheses*, Heck, R. F., Academic, New York, 1985.

[27] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

[28] Stille, J. K. in *The Chemistry of the Metal-Carbon Bond, Vol 2*, Hartley, F. R., Patai, S., Eds., Wiley, New York, **1985**, chap. 9, pp. 625-787.

[29] Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541-1547.

[30] Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923-6926.



Scheme IV

Furthermore, reductive elimination is a slow process as it has been reported for σ-alkyl-π-allyl-Pd(II) and bis-π-allyl-Pd(II) complexes.[31] In many cases this process can be accelerated by the addition of species capable of stabilizing the low-valent state of the metal, typically ligands with π-acceptor properties. Thus the choice of an additive with suitable coordinating properties could facilitate this step.

Despite of these problems, some examples of alkyl–alkyl coupling reactions have been reported (more detailed discussion about nickel-catalyzed alkyl–alkyl coupling can be found in the next section of the introduction, *section IIe*). The coupling reaction of Grignard reagents with haloalkanes catalyzed by copper salts is probably the most studied of such processes,[4] but the use of organometallic species that are less reactive than Grignard reagents would extend this method of bond formation to more highly functionalized substrates. In this sense, the low regioselectivity giving a mixture of internal and terminal coupling products on the reaction of allylic electrophiles and the slow reductive elimination from σ-alkyl-π-allyl- or di-π-allylpalladium species[26,32,33] are also pending subjects in synthetically useful catalytic transformations.

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31 Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779-5789.

4 (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1483-1487. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351-360.

26 *Palladium Reagents in Organic Syntheses*, Heck, R. F., Academic, New York, 1985.

32 Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691-694.

33 Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620-3628.

Some proposals have been developed in order to solve this problem related to alkyl–alkyl bond formation. Thus, it has been found that various phosphine ligands are effective in stabilizing the Pd(0) or Ni(0) intermediates. Changes in the stoichiometry, size, and electronic effects of the phosphines, all these contribute to the reactivity of catalysts toward oxidative addition and reductive elimination. In many cases triphenylphosphine is satisfactory ligand. However a number of ligands have been designed and synthesized to attain high catalyst efficiency or selectivity and to expand the scope of the reaction. Bisphophines having large P–M–P angle, such as dppp, dppb, and dppf, were designed to minimize *β*-hydride elimination in $C(sp^3)$–$C(sp^2)$ coupling of alkylmetals. Bulkiness of phosphines, such as $(t\text{-Bu})_3P$, Cy_3P or 2-(di-*t*-butylphosphino)biphenyl, were recognized to be highly reactive for oxidative addition, thus allowing the coupling reactions of chloroarenes with palladium catalysts.[34]

Ic. A concise overview on the most versatile and extensively used metal-catalyzed cross-coupling reactions

The continuous search for biologically active molecules for the pharmaceutical and agrochemical industries is one of the largest areas of research in which synthetic organic chemistry plays a fundamental role. Since most molecules with biological activity, even natural products of commercial use, are synthesized in chemical laboratories, there is a constant demand for the development of new methods for selective C–C bond formation. Additionally, the chemistry of materials needs effective methods for the tailored construction of a wide variety of structures. Such procedures should ideally be mild and highly tolerant towards a wide range of functional groups. At the same time the chemo-, regio-, and stereoselective formation of new C–C bonds is one of the major goals of organic chemistry.

Organometallic reagents are particularly well suited for such reactions since the polarity of the carbon–metal bond of these reagents confers a nucleophilic character to the carbon atom bound to the metal and allows reactions with a variety of carbon-

[34] (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561. (c) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

centered electrophiles furnishing cross-coupled products. Thus, the nature of the metal or of the metallic moiety (ML_n) is exceedingly important for tuning the reactivity. As illustrated in **Figure 1**, the reactivity of organometallic species towards electrophilic species increases with the ionic character of the carbon–metal bond. A classification of the transition metal-catalyzed cross-coupling reactions can be done according to the organometallic species used as nucleophile. Usually every protocol is called by the name of the main investigator responsible for its discovery and subsequent progress. Thereby, the Negishi coupling (or reaction or protocol) may loosely be defined as the Pd- or Ni- catalyzed cross-coupling through the use of organometals containing metals of intermediate electronegativity, such as Zn (1.6), Al (1.5), and Zr (1.4). Other examples include nucleophiles containing Si (Tamao-Kumada, Hiyama-Hatanaka), B (Suzuki-Miyaura), Sn (Migita-Kosugi, Stille), Al (Nozaki-Oshima, Negishi), Mg (Kumada-Tamao, Corriu), etc.

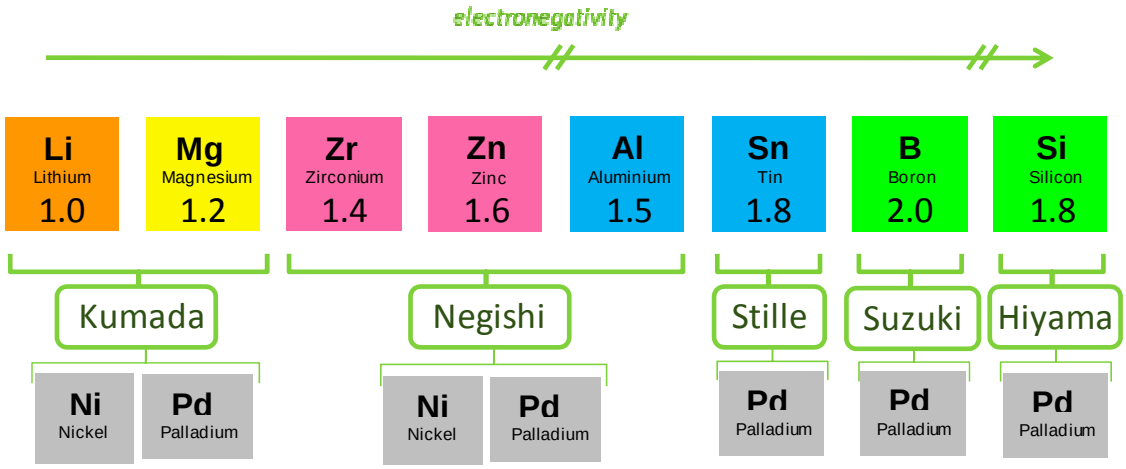


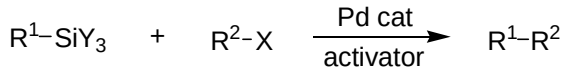
Figure 1

Obviously, less nucleophilic and basic character of the nucleophile allows conducting the cross-coupling reactions with higher chemosectivity. The use of highly reactive species, as organolithium reagents, often compromises selectivity and tolerance towards sensitive functional groups. On the other hand, the reaction of the less reactive organometallic species, such as organozinc, organotin, or organoboron compounds, must be necessarily promoted by using transition metal catalysts to give access to the

broad field of the transition metal-catalyzed transformations.[1] Organomagnesium reagents, which show lower reactivity towards electrophiles than the corresponding organolithium reagents, have still a high-enough reactivity toward many electrophiles with a remarkable functional-group tolerance at low temperature.[35]

Ic.1. *Cross-coupling reactions with Si, B, Sn, Zr and Al organometallics.*

Organosilicon reagents have many of the suitable properties of the nucleophiles used for cross-coupling reactions, such as including availability, low toxicity, and high functional-group compatibility. Environmentally benign and of low molecular weight, silicon may be an ideal donor of organic groups in a cross-coupling reaction. **Scheme V** summarizes the silicon-based cross-coupling, now simply called *Hiyama coupling*, and demonstrates that a variety of organic groups on Si are applicable to the reaction. In 1982 Kumada, Tamao and their coworkers reported palladium-catalyzed disilylative coupling of organosilanes with aryl halides.[36] Hiyama contributed enormously in overcoming the limitations related to the low polarization for C–Si bond and exploring the scope of the cross-coupling reactions to various substrates.[37]



R^1= alkyl, aryl, alkenyl, alkynyl

R^2 = allyl, aryl, alkenyl

X = Cl, Br, I, OSO_2CF_3,OCO_2Et

Pd cat: $(\eta^3\text{-}C_3H_5PdCl)_2$, $Pd(PPh_3)_4$

Y_3 = Me_3, Me_2F, MeF_2, F_3

activator = TBAF, KF, NaOH, (RO^-)

Scheme V

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[1] (a) *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **1998**. (b) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, **2004**.

[35] *Handbook of Functionalized Organometallics*, Knochel, P.; Krasovskiy, A; Sapountzis, I. Wiley-VCH, Weinheim, **2005**, *1*, 109.

[36] Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542-549.

[37] (a) Hiyama T. *J. Organomet. Chem.* **2002**, *653*, 58-61. (b) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918-920. (c) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268-270. (d) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299-301.

More recently, Fu and coworkers developed a method for accomplishing room-temperature Pd/PR_3-catalyzed Hiyama cross-couplings of unactivated alkyl bromides and iodides.[38] Further increasing the scope of cross-coupling reactions with secondary alkyl electrophiles, Powell and Fu developed a nickel-catalyzed coupling of aryl trifluorosilanes. In this method, a Ni^{II}/bathophenanthroline catalyst system is used for the cross-coupling in the presence of CsF.[39] The use of a nickel(0) source led to a drop in yield, and palladium did not promote the reaction. A variety of cyclic and acyclic secondary bromides and cyclic iodides can be used, and the substrates can contain ether, imide, ketone, and carbamate functional groups. Fu and co-workers later developed a more active catalyst system.[40] The use of norephedrine as the ligand enables the coupling of unactivated secondary bromides and iodides in much higher yield than with the first-generation $NiBr_2$/bathophenanthroline catalyst system. Furthermore, this system catalyzes the reaction of activated secondary alkyl chlorides and thus expands the scope of the Hiyama coupling significantly.

In continuation recently Fu and coworkers reported that nickel/diamine catalyst accomplishes asymmetric Hiyama reactions of α-bromo esters with aryl silanes to provide α-aryl esters in good enantiomeric excess; this method can also be applied to enantioselective alkenylation reactions.[41]

In 1978, Negishi reported that iodobenzene selectively coupled with the 1-alkynyl group on lithium l-hexynyl(tributyl)borate through a palladium-catalyzed addition-elimination sequence (Heck-type process); however, the cross-coupling reaction of organoboron compounds, which involves the transmetalation to palladium(II) halides as a key step, was found to proceed smoothly when these were activated with suitable bases. This methodology has proven to be a quite general technique for a wide range of selective C−C bond formation.[42]

Organoboron compounds are highly electrophilic, but the organic groups on boron are weakly nucleophilic, thus limiting the use of organoboron reagents for the

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[38] Lee, J. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616-5617.

[39] Powell, D. A.; Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788-7789.

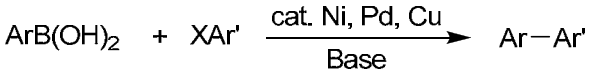
[40] Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 3556-3558.

[41] Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302-3303.

[42] (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178-184. (b) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743-4748.

ionic reactions. However, the coordination of a negatively charged base to the boron atom has been recognized to be an efficient method of increasing its nucleophilicity to transfer the organic group on boron to the adjacent positive center (1,2-migration reaction). Fortunately, organoboron compounds, even organoboronic acids and esters, have sufficiently enough reactivity for the transmetalation to other metals. Thus, transmetalations to magnesium(II),[43] zinc(II),[44] aluminum(II),[45] tin(IV),[46] and copper(I)[47] halides have been extensively studied.

The metal-catalyzed cross-coupling reaction between organoboron compounds and organic halides or triflates is called the *Suzuki coupling*, *Suzuki reaction*, or *Suzuki–Miyaura coupling* (**Scheme VI**).[48]



Scheme VI

The availability of reagents and the mild reaction conditions all contribute to the versatility of this reaction. The coupling reaction offers several additional advantages, such as being largely unaffected by the presence of water, tolerating a broad range of functional groups, and proceeding generally regio- and stereoselectively.[48] Moreover, the inorganic by-product of the reaction is non-toxic and easily removed from the reaction mixture thereby making the Suzuki coupling suitable not only for laboratories but also for industrial processes.

As it happens with other cross-coupling reactions, the coupling of alkyl halides has been more recently developed. For example, recently, Asensio and co-workers have

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[43] Kondo, R; Murahashi, S. *Tetrahedron Lett.* **1979**, *12*, 1237-1240.

[44] (a) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593-1594. (b) Agrios, K. A.; Srebnik, M. *J. Organomet. Chem.* **1993**, *444*, 15-20.

[45] Giacomelli, G.; Menigagi, R.; Caporusso, A. M.; Lardicci, L. *J. Org. Chem.* **1978**, *43*, 1790-1793

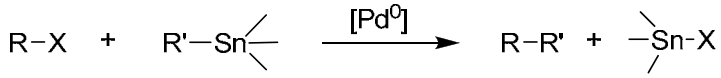
[46] George, T. A.; Lappert, M. F. *J. Chem. Soc. Chem. Comm*. **1966**, 463-464.

[47] (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* **1977**, *99*, 5652-5656. (b) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 550-552.

[48] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

reported a palladium-catalyzed Suzuki coupling reaction of activated secondary bromo sulfoxides with an array of aryl boronic acid.[49]

The cross-coupling of organotin reagents with a variety of organic electrophiles, catalyzed by palladium, called as *Stille reaction*, also provides a method for generating a C–C bond (**Scheme VII**). Because this mild, versatile reaction is tolerant to a wide variety of functional groups on either coupling partner, is stereospecific and regioselective, and gives high yields of product, it is ideal for use in the synthesis of elaborate organic molecules.[50]



Scheme VII

When the coupling reaction is carried out in the presence of carbon monoxide, instead of a direct coupling, carbon monoxide insertion takes place, stitching the two coupling partners together and generating a ketone. Furthermore, diverse arrays of functionalized organostannanes are readily available by a number of different reaction types.[51] A variety of organic electrophiles undergo the cross-coupling reaction, the aryl halides being one of the most thoroughly studied.[52] Usually aryl iodides and bromides lead to coupled products under mild conditions, while aryl chlorides require activation with electron-withdrawing substituents.

In 1976 Negishi developed highly selective procedures for the synthesis of olefins which involve the reaction of alkenylaluminium or alkenylzirconium derivatives

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[49] Rodríguez, N.; Ramírez de Arellano, C.; Asensio, G.; Medio-Simón, M. *Chem. Eur. J.* **2007**, *13*, 4223-4229.

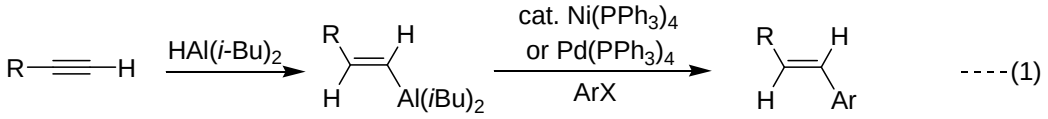
[50] Review on the Stille reaction: (a) Farina, V.; Krishnamurthy, V.; Scott, W. K. *Organic Reactions* Vol. 50, Wiley, New York, **1997**; for a review on the allyl-allyl coupling, see: (b) Méndez, M.; Echavarren, A. M. *Eur. J. Org. Chem.* **2002**, 15-28.

[51] (a) Stille J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524. (b) Mitchell, T. N. *J. Organomet. Chem.* **1986**, *304,* 1-16.

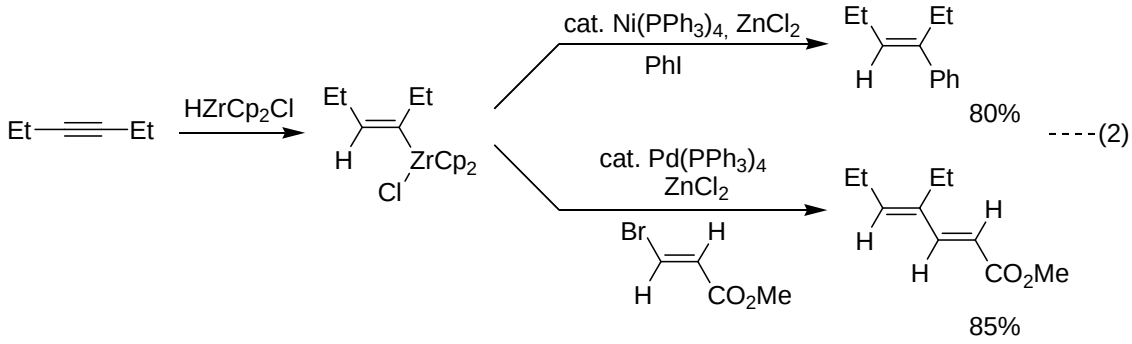
[52] (a) Yokoyama, Y.; Ito, S.; Murakami, Y. *Tetrahedron Lett.* **1985**, *26,* 6457-6460. (b) Biley, T. R. *Tetrahedron Lett.* **1986**, *27*, 4407-4410. (c) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422-424.

with unsaturated organic halides in the presence of a Pd(0)-phosphine or Ni(0)-phosphine complex used in place of organomagnesium reagents.[53]

In the cases where the Pd- or Ni-catalyzed cross-coupling reactions of alkenylaluminium and alkenylzirconium derivatives are sluggish, addition of Zn salts (e.g., $ZnCl_2$ and $ZnBr_2$) significantly accelerated these reactions in many cases (double metal catalysis).[54] Some 25 years after the discovery of beneficial effects of Zn salts, $InCl_3$ has shown to be an effective co-catalyst, superior to $ZnCl_2$ or $ZnBr_2$ in promoting the Pd(DPEphos)Cl_2-catalyzed cross-coupling of alkenylmetals containing Al or Zr via hydrometalation or carbometalation with 1,2-dihaloethylenes (**Scheme VIII**).[55]



R = *n*-Bu, ArX = 1-NaphBr: 93%. R = *c*-Hex, ArX = *p*-TolBr: 75%



Scheme VIII

The first Pd(acac)$_2$-catalyzed Negishi cross-coupling of alkenylzirconium reagents with alkyl electrophiles under ligandless conditions has been recently reported.[56] Such ligandless processes are attractive from the standpoints of cost,

[53] (a) Baba, S. Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731. (b) Negishi, E.; Baba, S. *J. Chem. Soc. Chem. Comm.* **1976**, 596-597.

[54] Negishi, E.; Okukado, N.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254-2256.

[55] Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531-1534.

[56] Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82-83.

simplicity and ease of purification. The Zr-catalyzed methylalumination of heterosubstituted arylethynes containing O, S, Cl, and Si, has also been reported.[57]

The use of organozinc and organomagnesium reagents provides additional possibilities for realizing cross-coupling. As our efforts have been focused on the study of nickel-catalyzed cross-coupling reaction of organic halides with these two kinds of organometallic reagents, the background and recent advances on their use for the transition metal-catalyzed cross-coupling reactions will be discussed in the next sections.

Although our approach to the cross-coupling reaction of organic halides with organozinc and organomagnesium reagents involves the use of nickel complexes as the catalysts, palladium-catalyzed Negishi and Kumada cross-coupling reactions have been much more extensively developed. With the aim of not to overlook completely this fact, a very brief mention to the origin and the advances on palladium-catalyzed Negishi and Kumada cross-coupling reactions using organozinc and organomagnesium reagents, respectively, will be included in the next two sections.

Ic.2. *Pd-catalyzed Negishi cross-coupling reaction with organozinc reagents*

Although, as mentioned previously, highly reactive organomagnesium and organolithium reagents are very beneficial to organic synthesis, they have some drawbacks, such as low chemosectivity and very poor functional group tolerance. One of the first alternatives to the frequently undesired high reactivity of organolithium and organomagnesium reagents was found between 1970 and 1980, by performing reactions with organozinc reagents which led to highly chemoselective processes. It was soon pleasantly noticed that organozincs, although very unreactive with most organic electrophiles, smoothly undergo transmetallations[58] with a variety of transition metal salts or complexes leading to new transition-metal compounds which then react with a range of organic electrophiles due to the presence of *d*-orbitals which allow new reaction pathways that are available to main group organometallics (**Scheme IX**).[59] This

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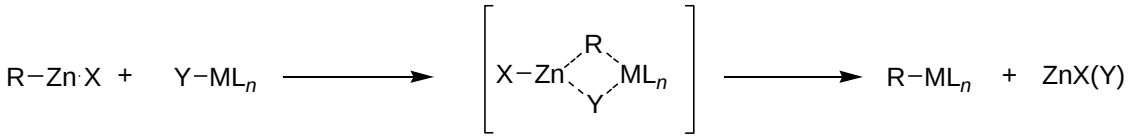
[57] Wang, G.; Zhu, G.; Negishi, E. *J. Organomet. Chem.* **2007**, *692*, 4731-4736.

[58] (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348. (b) Knochel, P.; Yen, M. C. P.; Berk, S. C.; Yalbert, J. *J. Org. Chem.* **1988**, *53*, 2390-2392.

[59] Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117-2188.

particular behaviour encouraged the use of organozinc reagents as suitable nucleophiles for transition metal-catalyzed cross-coupling reactions.



M = Ti, Mo, Ta, Nb, V, Pd, Ni, Pt, Cu .....

Scheme IX

In addition, diorganozincs (R_2Zn), which were important reagents for the general enantioselective preparation of polyfunctional secondary alcohol from aldehydes,[60] showed higher reactivity than organozinc halides,[61] undergoing transmetallation reactions more readily.

During the last decade, the Pd-catalyzed cross-coupling reactions have greatly proliferated and the examples of this process have been very numerous. For instance, the Pd-based catalysis has allowed the cross-coupling reaction of alkenyl halides with arylzinc reagents.[62] The Pd-catalyzed cross-coupling of aryl halides with arylzinc reagents has also been sufficiently explored.[63] Among all the studies carried out on this type of cross-coupling reactions the recent work of Fu *et al.* should be emphasized, since the authors achieve a wide array of cross-coupling reactions of unactivated alkyl electrophiles with alkyl-, alkenyl-, and arylzinc reagents by means of Pd/trialkylphosphine-based catalysts.[64]

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[60] Knochel, P.; Vettel, S.; Eisenberg, C. *Appl. Organomet. Chem.* **1995**, *9*, 175-188.

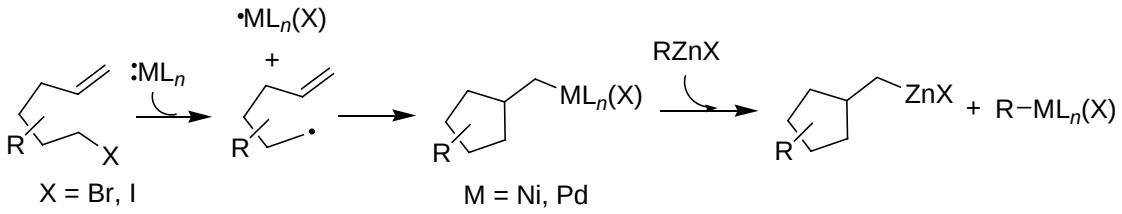
[61] Knochel, P. *Synlett.* **1995**, 393-403.

[62] For some recent examples see: (a) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G.; *Tetrahedron*, **1996**, *52*, 7201-7220. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724. (c) Kabir, M. S.; Monte, A.; Cook, J. M. *Tetrahedron Lett.* **2007**, *348*, 7269-7273.

[63] For some recent examples of Pd-catalyzed $C(sp^2)$–$C(sp^2)$ cross-soupling see: (a) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2723. (b) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028-13032. (c) Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593-2595. (d) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *Org. Lett.* **2008**, *73*, 7380-7382. (e) Manolikakes, G.; Dong, Z.; Mayr, H.; Li, J.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 1324-1328.

[64] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527-12530.

Another remarkable example is the treatment of an unsaturated alkyl halide with a Pd(0) or Ni(0) complex, which produces, by one electron transfer, a paramagnetic Ni(I) or Pd(I) complexes $ML_n(X)$ (M = Ni, Pd) and a radical intermediate that undergoes a smooth cyclization reaction and produces, after recombination with the transition-metal moiety, the nickel(II) or palladium(II) species. After transmetallation with zinc(II) salt, a stable organozinc cyclopentylmethyl derivative is produced (**Scheme X**). Then the resulting zinc organometallic can be transmetalated with CuCN·2LiCl, and it subsequently reacts with a broad range of electrophiles such as alkynyl halides, ethyl propionate, 3-iodo-2-cyclohexen-1-one, and nitroalkenes.[65]



Scheme X

Negishi also reported the Pd-catalyzed *trans*-selective monoalkenylation of 1,1-dibromoalkenes with 1-alkenylzinc derivatives to give 2-bromo-1,3-dienes, further substitution of Br with methyl-, higher alkyl-, and phenyl-zinc reagents under Pd-catalysis conditions produced diverse 1,3-dienes.[66]

As mentioned previously, Pd-complexes containing bisphophines having large P–M–P angle, such as dppp, dppb, and dppf, or bulky phosphines, such as $(t\text{-Bu})_3P$, Cy_3P or 2-(di-*t*-butylphosphino)biphenyl, have allowed to minimize *β*-hydride elimination in $C(sp^3)$–$C(sp^2)$ coupling of alkylmetals. In this way, the Pd-catalyzed Negishi coupling of alkylzinc halides, where the *β*-hydride elimination pathway is the

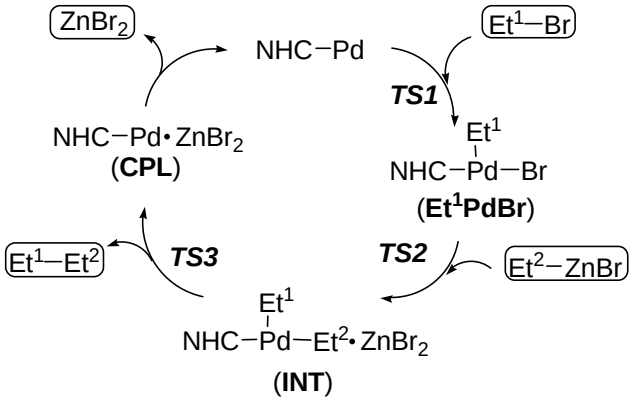
[65] (a) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *113*, 7027-7028. (b) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 231-232. (c) Stadtmüller, H.; Vapuel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204-1220.

[66] Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 2259-2263.

dominating process under standard conditions, could be efficiently performed with a wide range of aryl electrophiles.[67]

The catalyzed procedures by palladium complexes containing heterocyclic carbene ligands (Pd-NHCs) have notably contributed to the Negishi cross-coupling reactions. This catalytic system has proved to be useful for the achievement of room-temperature Negishi cross-couplings with unactivated primary bromides and alkyl organozinc reagents containing a variety of functionality.[68]

Interestingly, a novel mechanism has been proposed for alkyl–alkyl Negishi cross-coupling by Pd/1,3-(2,6-diisopropylphenyl)imidazolyl-2-ylidene based on computational studies made by Organ and coworkers (**Scheme XI**).[69]



Scheme XI

The fast *anti*-oxidative addition possibly forms the intermediate (**Et^1PdBr**), which is the most energetically favourable due to coulombic repulsion between the NHC and Br^1 (ΔG^0_{298}=–53.9 KJ mol^{-1}). The transmetalation step is the rate determining step for the catalytic cycle. In **TS2**, Et^2 is being transferred to Pd at the vacant 'top'

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[67] Recent reports on Pd-catalyzed coupling of aryl halides and alkylzinc halides: (a) Bartrum, H. E.; Adams, H.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 3701-3712. (b) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923-3925. (c) Liu, Q.; Duan, H.; Luo, X.; Tang, Y.; Li, G.; Huang, R.; Lei, A. *Adv. Synt. Catal.* **2008**, *350*, 1349-1354. (d) Wang, H.; Liu, J.; Deng, Y.; Min, T.; Yu, G.; Wu, X.; Yang, Z.; Lei, A. *Chem. Eur. J.* **2009**, *15*, 1499-1507. (e) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532-7533.

[68] Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805-3807.

[69] Chass, G. A.; O'Brien, C. J.; Hadei, N.; Kantchev, E. A. B.; Mu, W. -H.; Fang, D. -C.; Hopkinson, A. C.; Csizmadia, I. G.; Organ, M. G. *Chem. Eur. J.* **2009**, *15*, 4281-4288.

position, whereas Br^1 is starting to bond to Zn from its *syn* position and Et^1 outwards and away from the Zn atom, which now reenters the coordination sphere of Pd. **TS3** is less crowded, and *i*-Pr-H-Pd interactions appear again to assist in pushing away the product molecule. The authors propose that *the presence of $ZnBr_2$ in the coordination sphere of the Pd atom during and beyond the reductive elimination provides additional steric interactions that may aid the expulsion of the cross-coupling product*, contrary to the general accepted mechanism which requires $ZnBr_2$ to dissociate prior to commencement of reductive elimination, and suggesting that these processes may not be discrete steps. The Pd–Zn interaction persists even after the departure of the cross-coupling product. The adduct between the highly electron-rich NHC–Pd(0) and the Lewis acidic $ZnBr_2$ is observed as an additional intermediate in the cycle (**CPL**).

Ic.3. *Pd-catalyzed Kumada cross-coupling reaction with Grignard reagents*

As previously mentioned, Kumada and colleagues[5a] and Corriu and Masse[6] demonstrated the synthetic utility of nickel cross-coupling reactions with these reagents. The main drawback at that time was the limited scope for the preparation of functionalized Grignard reagents. Neverthless, at the end of 1990s, it became clear that the carbon−magnesium bond is compatible with a number of sensitive electrophilic functional groups.[70]

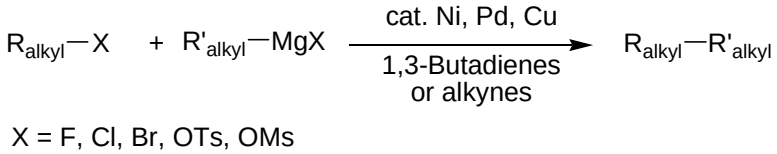
Kambe and co-workers found a new catalytic system for transition metal-catalyzed cross-coupling reactions using alkyl halides by use of an anionic complex. During the course of this study, they demonstrated that an anionic Ni, Pd, or Cu complex plays an important role in cross-coupling reactions of alkyl halides with Grignard or organozinc reagents in the presence of a π-carbon (for instance, dienes) as a ligand (**Scheme XII**).[71] This catalytic system tolerates a wide variety of functional groups, including nitriles, ketones, amides, and esters.

[5a] Tamao, K; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376.

[6] Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, *3*, 144-145.

[70] Boymond, L.; Rottländer, M.; Caliez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703.

[71] Terao, J; Kambe, M. *Acc. Chem. Res.* **2008**, *41*, 1545-1554.



Scheme XII

In this way, alkyl halides have now become even more promising candidates as substrates in transition metal-catalyzed reactions. The cationic and anionic transition metal complexes have been widely used as catalysts for organic synthesis at both bench and industrial scale, while synthetic applications of anionic complexes are less well-developed. Anionic complexes, formed by the reaction of neutral complexes with organometallic reagents, possess high electron densities. Consequently, it is expected that the nucleophilicity at the metal center or π-carbon ligands, as well as the electron-donating ability of the anionic complexes, would be enhanced in comparison with the corresponding neutral complexes.

In addition, the asymmetric cross-coupling of secondary alkylmagnesium and zinc reagents with aryl and alkenyl halides, in the presence of nickel or palladium catalysts coordinated with chiral phosphine ligands, have provided optically active cross-coupling products.[72] Not only nickel and palladium catalyze Kumada cross-coupling reaction but also other metals like copper and iron complexes have been shown to catalyze these couplings. Copper catalysis catalyzes the cross-coupling of primary and secondary alkyl halides with aryl magnesium reagents.[73] Iron catalyzed Kumada cross-coupling of secondary alkyl halides with aryl, alkenyl and alkyl Grignard reagents covers a wide range of formation of C–C bonds.[74]

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[72] Hayashi, T. *J. Organomet. Chem.* **2002**, *653*, 41-45.

[73] (a) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4056-4059. (b) Frisch, A. C.; Rataboul, F; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403-409.

[74] (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374-5375. (b) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137-4139. (c) Nakamura, M,; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686-3687. (d) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640-5648. (e) Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955-3957. (f) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886-1889. (g) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6521-6524. (h) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773-8787.

There are also recent reports of Pd-catalyzed Kumada cross-coupling between unsaturated (aryl and alkenyl) halides and arylmagnesium reagents.[75] Air-stable Pd(II) complexes bearing phosphinous acid ligands are efficient catalysts for cross-coupling of unactivated aryl chlorides with aryl Grignard reagents at room temperature to yield biaryls in high yield.[76] Palladium-catalyzed Kumada-Corriu coupling of alkylvinyl, arylvinyl and *O*-cyclohexenyl phosphate with aryl Grignard reagents have been succesfully developed under ligandless conditions at room temperature.[77]

II. Nickel-catalyzed cross-coupling reactions for the formation of C–C bonds.

The following section describes the most important achievements in nickel-catalyzed cross-coupling reactions for the formation of C–C bonds, being mainly focused on the use of organozinc and organomagnesium reagents as the nucleophiles and a variety of organic halides as the electrophiles.

IIa. C(sp)–C bond formation

In this section it can be noticed that the C(sp)–C bond formation by means of Ni-catalyzed cross-coupling reaction with organozinc or Grignard reagents has not been a subject of great interest, mainly due to the easy and ready availability of the resulting products through diverse procedures such as the Sonogashira cross-coupling reaction, among others.

However, the easy coupling of benzonitriles with alkynylzinc reagents in the presence of $Ni(PMe_3)_2Cl_2$-based catalysts, to afford the respective arylalkynes in high yields, has been recently described (**Scheme XIII**).[78] Remarkably, this is one example

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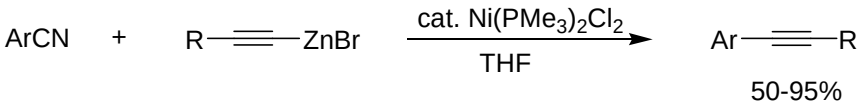
[75] (a) Zhang, L.; Cheng, J.; Zhang, W.; Lin, B.; Pan, C.; Chen, J. *Chem. Comm.* **2007**, *37*, 3809-3814. (b) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162-167. (c) Manolikakes, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 205-209. (d) Gu, S.; Chen, W. *Organometallics*, **2009**, *28*, 909-914. (e) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844-3845. (f) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364-9370.

[76] Li, G. Y. *J. Organomet. Chem.* **2002**, *653*, 63-68.

[77] Gauthier, D.; Beckendorf, S.; Gogsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536-3539.

[78] Penney, J. M.; Miller, J. A. *Tetrahedron Lett.* **2004**, *45*, 4989-4992.

of the use of C–CN bond in benzonitriles for nickel catalyzed activation and functionalization. So, from this point of view, they can also be considered as feasible substrates along with the aryl halides commonly employed in Negishi or Sonogashira alkynylation protocols.



Scheme XIII

Also the C(sp)–C(sp^3) bond formation has been recently carried out. Thus, Negishi *et al.*, while exploring the palladium-catalyzed cross-coupling reaction of alkynylzincs with benzylic electrophiles, observed that $Ni(PPh_3)_2Cl_2$ and $Ni(dppf)Cl_2$ catalyze the reaction of PhC≡CZnBr with $PhCH_2Br$ in THF to give PhC≡C–CH_2Ph although in low yield (ca. 30%).[79]

IIb. C(sp^2)–C(sp^2) bond formation

Aryl–aryl coupling has been achieved with both Ni and Pd catalysts using various metal nucleophiles. Aryl–aryl bonds are very often found in natural products such as alkaloids as well as in numerous biologically active parts of pharmaceutical and agrochemical specialities.

Nickel-catalyzed aryl–aryl bond formations have been studied especially since the discovery, by Kumada and Corriu, in 1972, of an efficient method for the formation of C–C bonds by nickel-catalyzed coupling of Grignard reagents with organohalides. This reaction was further developed by using complexes of Pd and is highly selective, allowing the formation of symmetrical and unsymmetrical biaryls in high yields under mild conditions. These types of reactions have been since then widely studied with, for example, organozinc, organoboron, and organotin reagents, showing similar high efficiency as well as improved compatibility with many functional groups present in the substrates.

In particular, the Mg-Ni, Mg-Pd, Zn-Ni, Zn-Pd, and B-Pd combinations have been extensively employed.

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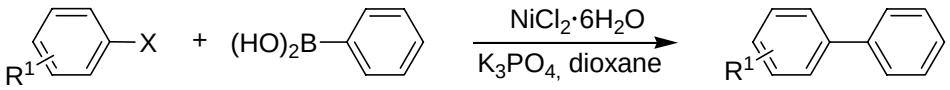
[79] Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927-2930.

Thus, several nickel-catalyzed cross-coupling reactions of aryl chlorides with aryl boronic acids to give biaryls have been reported.[80] Nickel-catalyzed Suzuki coupling of aryl mesylates and tosylates with aryl boronic acids using a nickel catalyst has been carried out in the presence of a reducing reagent.[81] Ni/C functions as an effective heterogeneous catalyst for Suzuki couplings. In most cases, a set of generalized reaction parameters (dioxane, temperature, K_3PO_4, LiBr, PPh_3) is enough to afford biaryl bond formation between functionalized aryl chlorides and various aryl boronic acids.[82]

Recently, a method for the Suzuki–Miyaura coupling reactions of aryl/alkenyl tosylates and mesylates with aryl and alkenyl boronic acids by using NHC-derived nickel(II)–pincer complexes has been described.[83]

Aryl bromides and iodides can be coupled with phenylboronic acid in good yields using $NiCl_2 \cdot 6H_2O$ as catalyst precursor.[84] This nickel complex is cheap, widely available and can be used without any auxiliary ligand or reducing agent. From a synthetic point of view this protocol is an easy alternative for the synthesis of biaryls from aryl bromides and iodides (**Scheme XIV**).



R^1=OCH_3, $COCH_3$, CF_3, CH_3
X = Br, I

Scheme XIV

[80] (a) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62,* 8024-8030. (b) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513-3516. (c) Zhou, L.; Miao, Q.; He, R.; Feng, X.; Bao, M. *Tetrahedron Lett.* **2007**, *48*, 7899–7902.

[81] (a) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447-3452. (b) Zim, D.; Lando,V. R.; Dupont, J.; Monteiro, A. L. *Org.Lett.* **2001**, *3*, 3049-3051.

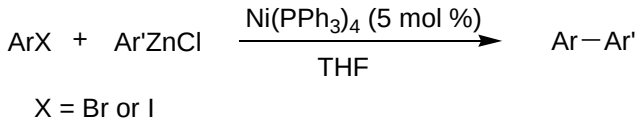
[82] Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139-2144.

[83] (a) Kuroda, J.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, *14*, 2251–2261. (b) Tang, Z.; Hu, Q. *J. Am. Chem. Soc*. **2004**, *126*, 3058-3059.

[84] Zim, D.; Monterio, A. O. *Tetrahedron Lett.* **2002**, *43*, 4009-4011.

Also several nickel(0)-triphenylphosphine or nickel–lithium halide complexes were found to enhance the rate of the cross-coupling reaction of aryl halides with allyl, vinyl and phenylacetylylstannanes.[85]

In particular, *Negishi reaction* has been widely used for the preparation of biaryl derivatives since the very beginning. Numerous examples of aryl–aryl coupling catalysed by transition metal complexes can be found in the literature, because of their generally good yields and their high functional group tolerance. In 1977, Negishi reported an aryl–aryl coupling reaction catalysed by Ni, thereby providing a general, convenient, and chemo- and regioselective route for synthesis of unsymmetrical biaryls (**Scheme XV**).[11a] $Ni(PPh_3)_4$ was prepared *in situ* by the reaction of $Ni(acac)_2$, PPh_3 and $(i\text{-Bu})_2AlH$ (1:4:1).



Scheme XV

The aryl–aryl coupling reaction proceeded smoothly at room temperature even with aryl halides containing electron-donating groups, such as methyl and methoxy, which generally react less readily with Ni(0) complexes than those containing electron-withdrawing groups. These conditions could be also used for the coupling of benzylzinc halides.

Unsymmetrical biaryl products were obtained in an efficient manner using inexpensive and readily available aryl chlorides as substrates in a Negishi-type cross-coupling reaction with arylzinc reagents via either Ni-catalysis (**Scheme XVI**).[86] The inherently mild nature of the arylzinc reagents utilized in this chemistry makes the process particularly attractive for the synthesis of biaryl compounds containing "reactive" functionality (e.g., nitrile, carbonyl, ester groups). In addition, this biaryl synthesis is advantageous, relative to the Stille or Suzuki biaryl protocols, since the arylzinc reagents are not isolated prior to use, but instead they are prepared and utilized *in situ*.

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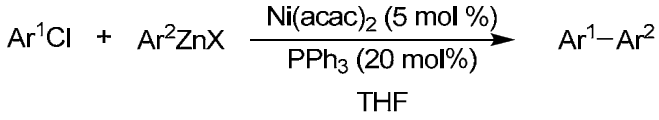
[85] Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis*, **1998**, *10*, 1544-1549.

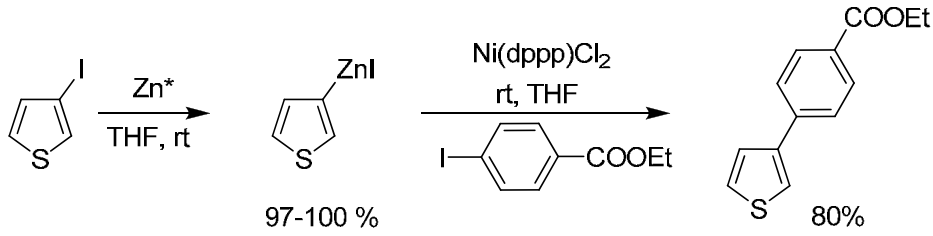
[11a] Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823.

[86] Miller, J. A.; Farrell, R. P. *Tetrahedron Lett*, **1998**, *39*, 6441-6444.



Scheme XVI

Rieke *et al*.[87] were interested in the chemistry of *β*-substituted thiophenes, very useful chemical compounds for both the materials and pharmaceutical sciences. One of the most used procedures for preparing these substrates involved the formation and subsequent reaction of 3-thienyl organometallics with electrophiles. Thus, Rieke zinc (Zn*) was prepared through the reduction of $ZnCl_2$ by Li using naphthalene as an electron carrier in THF. The activated metal then underwent oxidative addition to 3-iodothiophene to form 3-thienylzinc iodide as a regiostable reagent in THF at room temperature. This substrate allowed the cross-coupling reactions with different aromatic halides using Ni(dppe)Cl_2 as the catalyst (**SchemeXVII**). As already observed with other compounds, the reactivity of the organozinc species was found to be substrate dependent and aromatic halides with an electron-withdrawing group in the *para* position were found to be more active than the corresponding halides with an electron-donating group (*p*-tolyliodide led to the corresponding 3-tolylthiophene with only a 40% yield).

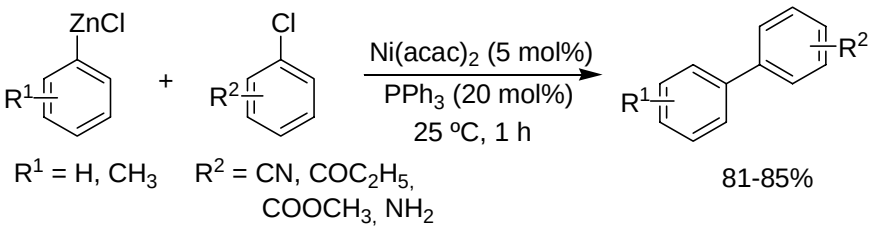


Scheme XVII

Tucker and Vries in 2002, while exploring palladium catalysed coupling of alkylzinc reagents with aryl chlorides, found that Ni-based catalysts (Ni(acac)$_2$/PPh_3) facilitate the coupling between aryl chlorides and arylzinc chlorides leading to

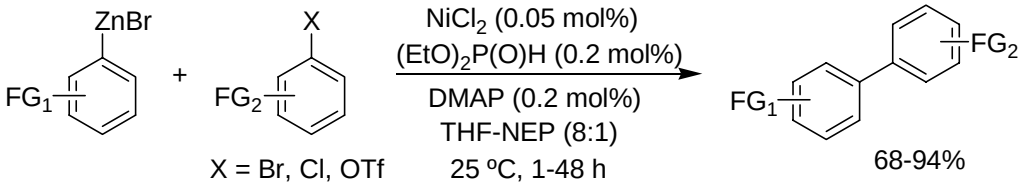
[87] Wu, X.; Rieke, R. D. *J. Org. Chem.* **1995**, *60*, 6658-6659.

formation of biaryl derivatives (**Scheme XVIII**).[88] With this catalytic system, coupling proceeded under very mild conditions, requiring only a few hours at 25 °C.



Scheme XVIII

Although organozinc halides tend to be sensitive to moisture and limitations exist regarding their preparation in the presence of some functional groups, they are still among the most useful coupling partners. Thus, Knochel has reported a very efficient catalytic system based on $NiCl_2$ and diethyl phosphinate/4-(dimethyl-amino)pyridine (DMAP) for the cross-coupling reaction between functionalised arylzinc bromides and aryl bromides, triflates, nonaflates and activated chlorides (**Scheme XIX**).[89] The optimal ratio of THF-NEP (*N*-ethylpyrrolidinone) after optimization turned out to be 8:1. A broad range of functionalised substrates reacted at room temperature, giving the cross-coupling products in good to excellent yields. An extremely small amount of transition metal catalyst (0.05 mol % Ni) in comparison with other methods was required.



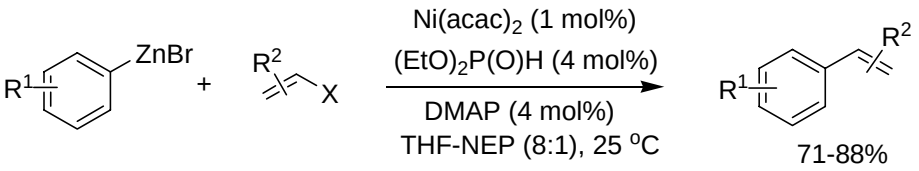
Scheme XIX

The reaction could be extended to the coupling of arylzinc halides with alkenyl halides and triflates in the presence of a higher amount of catalyst (1 mol% $Ni(acac)_2$, 4

[88] Tucker, C. E.; Vries, J. G. *Topics in Catálisis*, **2002**, *19*, 111-118.

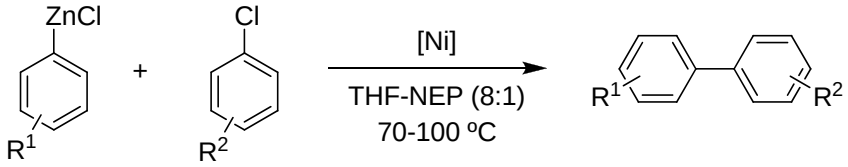
[89] Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871-4874.

mol% $(EtO)_2P(O)H$, 4 mol% DMAP, 1.3 equiv. ArZnBr, THF-NEP (8:1) (**Scheme XX**).[90]



Scheme XX

Wang and coworkers demonstrated amido pincer complexes of nickel to be highly active catalysts for the Negishi cross-coupling reaction. The catalysts were effective for the reactions of unactivated aryl chlorides and heteroaryl chloride with aryl and heteroaryl zinc reagents (**Scheme XXI**).[91] An extremely small amount of catalyst (1 mol%) was required in most cases, and the reaction displayed good functional group tolerance.



[Ni] = amido pincer complexes of nickel

R^2= OMe, NMe_2, C(O)Ph, COOEt, $C(O)NEt_2$ etc.

Scheme XXI

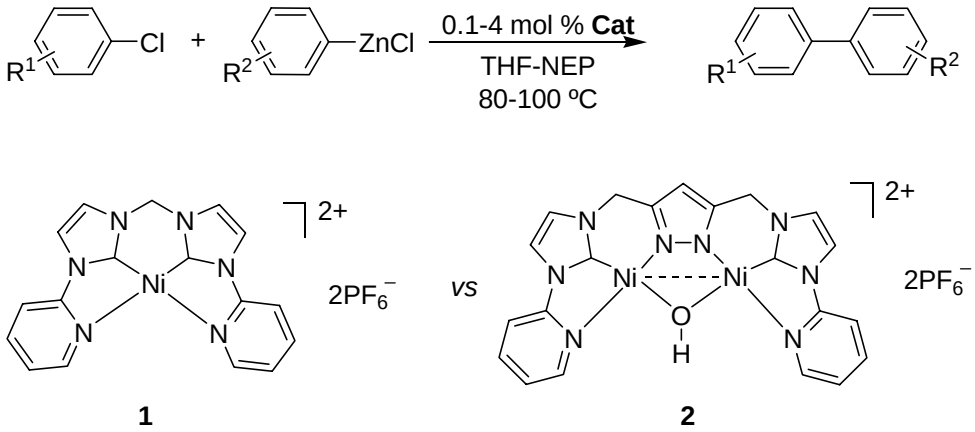
Chen and coworkers described the first successful Negishi cross-coupling catalyzed by mononuclear and binuclear nickel complexes supported by *N*-heterocyclic carbenes under mild conditions (**Scheme XXII**).[92] Both mononuclear and binuclear nickel-NHC complexes were effective for the coupling reactions of unactivated aryl chlorides, heterocyclic chlorides, and vinyl chloride with organozinc reagents leading to a wide range of biphenyls and terphenyls. The catalytic data showed that binuclear nickel-NHC complexes were more active than mononuclear nickel-NHC complexes

[90] Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521-7533.

[91] Wang, L.; Wang, Z. *Org. Lett.* **2007**, *9*, 4335-4338.

[92] Xi, Z.; Zhou, Y.; Chen, W. *J. Org. Chem.* **2008**, *73*, 8497-8501.

probably due to possible bimetallic cooperativity. All the Ni(II) complexes were air stable and could be easily prepared. These binuclear nickel-NHC catalytic systems could provide a complement to the protocols using expensive palladium and environmentally unfriendly phosphine or phosphite ligands in a number of organic transformations.



Scheme XXII

Very recently, Ni-based catalytic systems for the arylation of heteroarenes (azoles: thiazole, benzothiazole, oxazole, benzoxazole, and benzimidazole) with aryl halides and triflates have been established. $Ni(OAc)_2$/bipy is a general catalyst for aryl bromides/iodides, and $Ni(OAc)_2$/dppf is effective for aryl chlorides/triflates.[93]

Acyl halides can also be considered as feasible coupling partners for cross-coupling reactions. An efficient ketone synthesis protocol has been developed by cross-coupling of a variety of acyl fluorides, chlorides, anhydrides and thioesters and Ph_2Zn in the presence of $Ni(cod)_2$ and bipy.[94]

On the other hand and in relation to the use of organomagnesium reagents as nucleophiles, Corriu[6] described nickel(II) acetylacetonate to be the most effective catalyst for the coupling reactions between aromatic Grignard reagents and olefinic halides (various *trans*-stilbenes in high yields 50-75%). This team also reported the synthesis of *p*-terphenyl in an 80% yield (**Scheme XXIII**) by reacting *p*-dibromobenzene.

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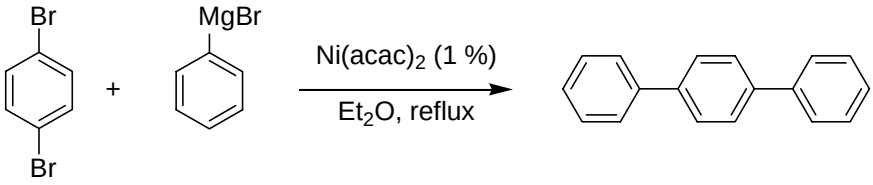
[93] Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733-1736.

[94] Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964-15965.

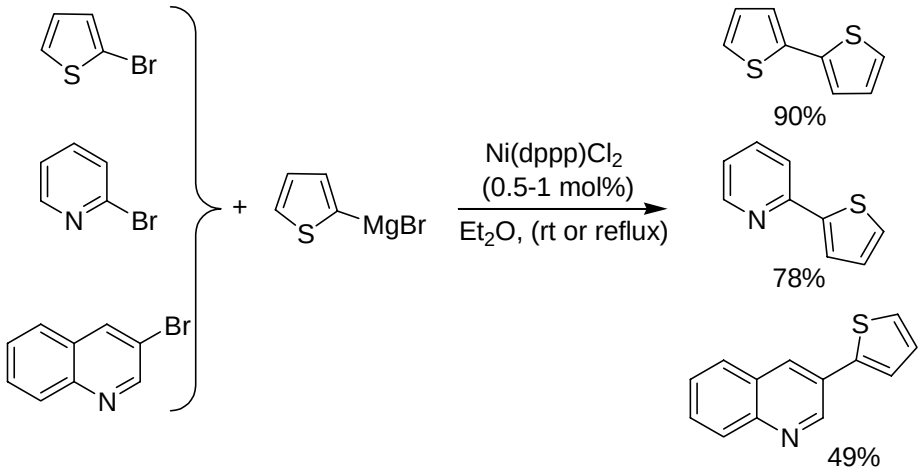
[6] Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Commun.* **1972**, *3*, 144-145.



Scheme XXIII

At the same time, Kumada studied this reaction by using dihalodiphosphinenickel complexes. His group found that bidentate diphosphine ligands exhibited remarkable catalytic activity (i.e. $Ni(dppp)Cl_2$ and $Ni(dppe)Cl_2$). They concluded that the *cis*-configuration of the two phosphine groups in the diorganonickel intermediate was of major importance. They especially noticed the high reactivity of chloride derivatives as a remarkable feature. This group later extended the scope of this nickel-catalyzed Grignard cross-coupling to numerous examples of the arylation of haloheterocyclic compounds.[95] In the presence of catalytic amounts of $[NiCl_2(dppp)]$, bromothiophenes, halopyridines, haloquinolines, and haloisoquinolines reacted with aryl (and also alkyl) Grignard reagents at either room or ether-refluxing temperature to give cross-coupling products. Some representative examples are reported in **Scheme XXIV**.

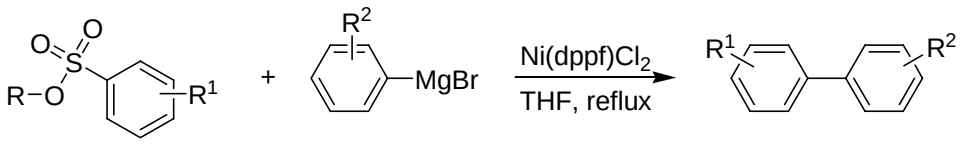
The authors found applications of this method for the synthesis of some substituted isoquinolines as precursors for the preparation of isoquinoline alkaloids of pharmaceutical interest, such as cryptostyline II.



Scheme XXIV

[95] Tamao, K; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, A. *Terahedron* **1982**, *38*, 3347-3354.

The nickel-catalyzed cross-coupling reactions of neopentyl arenesulfonates with arylmagnesium bromides, involving nucleophilic aromatic substitution of alkyloxysulfonyl groups by aryl nucleophiles, resulted in the formation of unsymmetrical biaryls in high yields (**Scheme XXV**).[96] Optimal efficiencies were obtained by adding 3 + 2 equiv of the Grignard reagent to a mixture of Ni(dppf)Cl_2 and the sulfonate in refluxing THF. Neopentyl arenesulfonates were useful sources of the electrophilic aryl groups in these transition metal-catalyzed cross-coupling reactions. Aryl sulfonates were inappropriate due to their ambident reactivity under the reaction conditions.



R = 2,2-dimethylpropyl, 4-ethylphenyl

R^1= 4-Me, 4-*t*Bu, 4-OMe, 2,4,6-*tri*-Me

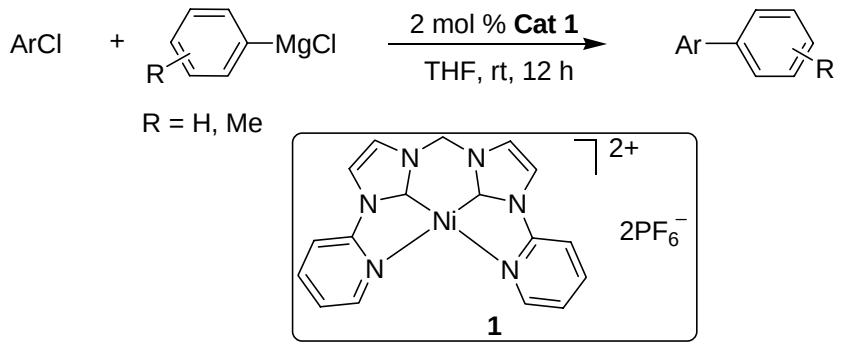
R^2= 2-Et, 4-Et, 4-*t*Bu, 4-OMe, 4-CF_3

Scheme XXV

More recently, Chen and coworkers have demonstrated that the nickel(II) complexes supported by multidentate NHCs are highly active catalysts for Kumada couplings reactions of various aryl chlorides at room temperature (**Scheme XXVI**).[97] The catalysts are economical, air-stable, and easily available. The high catalytic activities of these nickel complexes are probably due to the stabilization effect of the pyridine-functionalized bis(NHC) ligands on the catalytically active species by forming stable Ni-C bonds and the hemilability of the pyridine group on the metal. Room temperature reaction makes the coupling of the substrate, bearing substituents not compatible with Grignard reagents, possible.

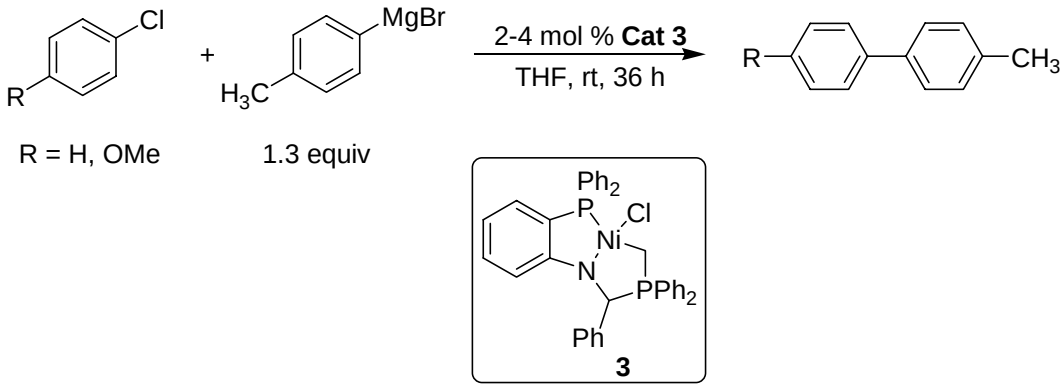
[96] Cho, C.; Yun, H.; Park, K. *J. Org. Chem.* **2003**, *68*, 3017-3025.

[97] Xi, Z.; Lui, B.; Chen, W. *J. Org. Chem.* **2008**, *73*, 3954-3957.



Scheme XXVI

Catalysis of the nickel complexes in the Kumada cross-coupling was also investigated by Wang and coworkers.[98] Reaction of *N*-benzylidene-2-(diphenylphosphino)benzenamine with Ph_2PCH_2Li · TMEDA generated [Li{N{CH(Ph)-CH_2PPh_2}C_6H_4(PPh_2)-2}]. Reaction of this Li-complex with $Ni(PEt_3)_2Cl_2$ afforded [Ni(Cl){N{CH(Ph)CH_2PPh_2}C_6H_4(PPh_2)-2}] (**3**). Complex **3** can efficiently catalyze cross-coupling reactions of *p*-MeC_6H_4MgBr with aryl halides, including unactivated and deactivated aryl chlorides (**Scheme XXVII**).



Scheme XXVII

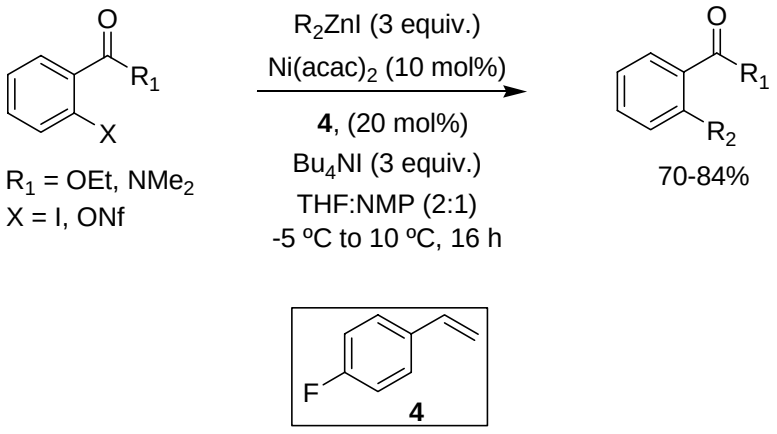
[98] Sun, K.; Wang, L.; Wang, Z. *Organometallics*, **2008**, *27*, 5649-5656.

IIc. C(sp^2)–C(sp^3) bond formation: coupling of C(sp^2) electrophiles

Ni-catalysed couplings involving aryl halides and benzylzinc halides were described by Negishi in his early reports on this reaction.[11a] Nevertheless, Pd-catalysed reactions have been usually chosen for the formation of alkyl–aryl bonds from aryl halides and pseudohalides.

Only a few examples of Ni-catalyzed Negishi reactions of aryl electrophiles for the formation of C(sp^2)–C(sp^3) bonds have been published to date, despite the alternative for this bond formation consisting on the use of alkyl electrophiles and arylzinc reagents has been traditionally disregarded due to the potential *β*-elimination of hydrogen on the intermediate alkylmetal complexes.[27]

Knochel reported that Ni(acac)$_2$/*p*-fluorostyrene (**4**)/Bu_4NI catalysis allows considerable improvement of the cross-coupling between *ortho*-substituted aryl iodides or nonaflates and a range of alkylzinc iodides (**Scheme XXVIII**, **Table 1**).[99] This nickel-catalyzed reactions proceeded well in solution and in the solid-phase.



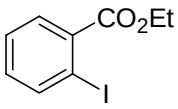
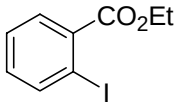
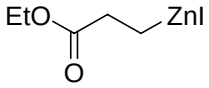
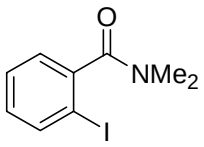
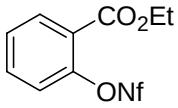
Scheme XXVIII

[11a] Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823.

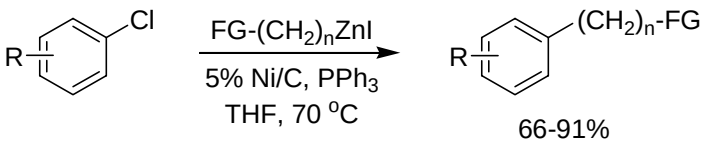
[27] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

[99] Jensen, A. E.; Dohle,W.; Knochel, P. *Tetrahedron* **2000**, *56*, 4197-4201.

Table 1. *Reactions of ortho-substituted aryl iodides or nonaflates and alkylzinc iodides*

Entry	*ortho*-substituted aryl iodides or nonaflates	Alkylzinc iodide	Yield (%)
1		PentZnI	79
2			83
3		PentZnI	73
4		PentZnI	84

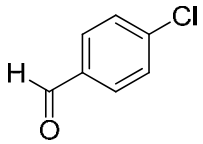
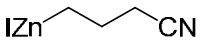
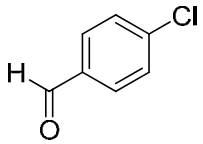
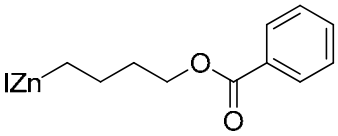
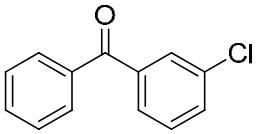
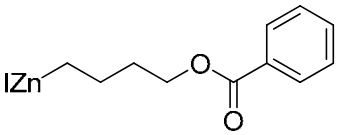
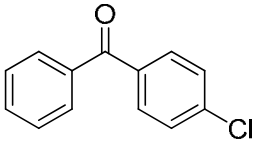
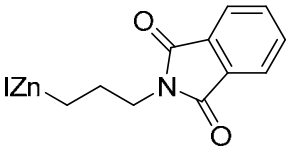
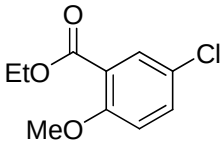
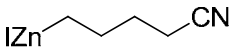
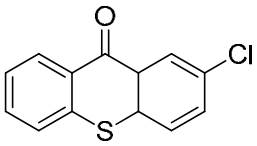
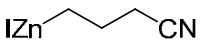
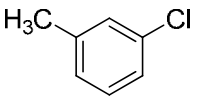
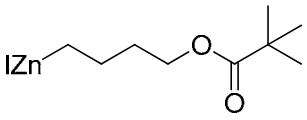
Also Ni/C was developed as an inexpensive, heterogeneous, and highly effective catalyst for mediating the efficient Negishi coupling between functionalised zinc reagents and substituted aryl chlorides (**Scheme XXIX**).[100] As with heterogeneous reactions in general, the simplicity in workup is especially attractive. Importantly, retention of nickel on the solid support offers control over such critical parameters as waste disposal and toxicity.



Scheme XXIX

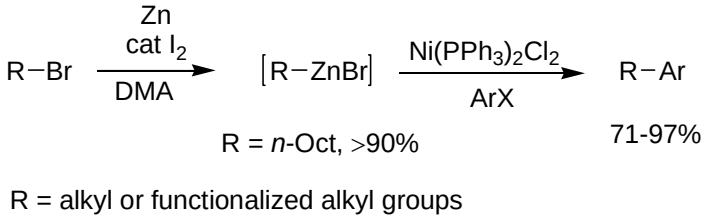
[100] Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819-5820.

Table 2. *Reactions of aryl chlorides with functionalised zinc reagent catalysed by Ni/C*

Entry	Aryl chloride	Alkylzinc reagent	Yield (%)
1			80
2			69
3			85
4			66
5			84
6			72
7			91

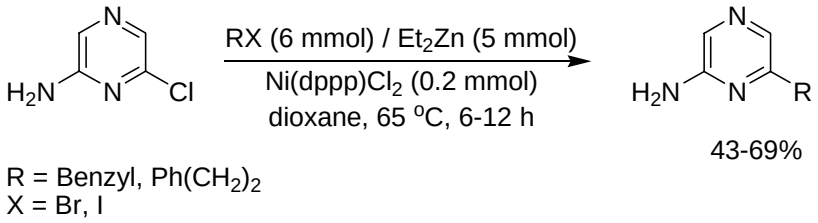
A variety of substituted alkyl zinc halides and aryl chlorides with electron-deficient functional groups (**Table 2**) like aldehydes (entries 1 and 2), ketones (entries 3 and 4), esters (entry 5), and nitriles (entries 5 and 6), readily and efficiently couple in refluxing THF under these heterogeneous conditions. Particularly noteworthy is the example involving a sulphur-containing compound (entry 6).

Huo S. described an easy preparation of alkylzinc reagents from unactivated alkyl bromides and chlorides and its participation in Ni-catalyzed cross coupling reaction with aryl chlorides.[101] Alkylzinc bromides have been efficiently prepared by the direct insertion of zinc metal (dust, powder, granule, shot), activated with 1-5 mol % I_2, into alkyl bromides (oxidative addition) in a polar aprotic solvent. These organozinc reagents thus formed undergo Ni- and Pd-catalyzed cross-coupling with aryl halides to produce functionalized alkylarenes in excellent yields (**Scheme XXX**).



Scheme XXX

It has been shown that Ni-catalysis is capable of effecting the halogen-zinc exchange of primary alkyl halides with excess of diethylzinc. This raised the interesting prospect of using nickel catalyst [1,3-bis(di-phenylphosphino)propane]nickel(II) chloride for subsequent formation of alkylzinc halide *in situ* and its coupling to the chloropyrazine in a one-pot procedure (**Scheme XXXI**, **Table 3**).[102]

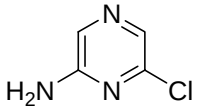
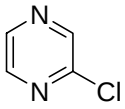
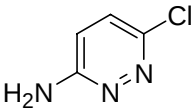
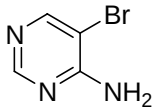
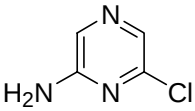
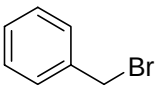
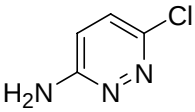
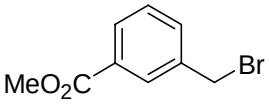


Scheme XXXI

[101] Huo, S. *Org. Lett.* **2003**, *5*, 423-425

[102] Walters, I. A. S. *Tetrahedron Lett.* **2006**, *47*, 341-344.

Table 3. *Reactions of amino heteroaryl chlorides for the formation of $C(sp^2)$–$C(sp^3)$ bond*

Entry	Amino-heteroaryl halide	Alkyl halide[a]	Yield (%)
1		$Ph(CH_2)_2I$	43
2[b]		$Ph(CH_2)_2Br$	42
3		$Ph(CH_2)_2Br$	60
4		$Ph(CH_2)_2Br$	52
5[c]			50
6			69

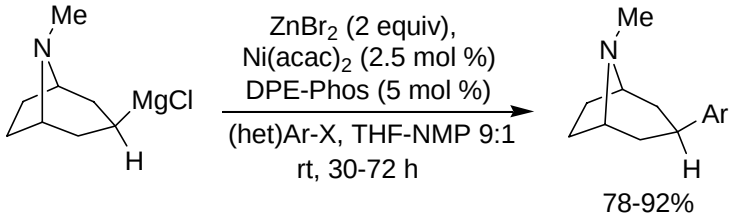
[a]Standard conditions: alkyl halide (6 mmol), diethylzinc (5 mmol) and $Ni(dppp)Cl_2$ (0.02 mmol) heated at 65 °C for 4 h in dioxane, amino-heteroaryl halide (1 mmol) added and refluxed for 2 h. [b]Standard conditions except alkyl halide (5 mmol), diethylzinc (3.5 mmol). [c]Standard conditions except alkyl halide, diethylzinc and $Ni(dppp)Cl_2$ heated at 100 °C for 4 h before addition of amino-heteroaryl halide (0.5 mmol).

It was found that halogen-zinc exchange could be brought about using a 20% excess of alkyl halide and 1M solution of diethylzinc. This allows the direct addition of the heteroaryl chloride for Negishi coupling without any intermediate manipulations such as evaporation of excess diethylzinc, resulting in a simple and convenient one-pot coupling process of amino-heteroaryl chlorides with alkylzinc reagents.

Finally, Ni-catalysed alkylation of arenes and heteroarenes by using aminoalkylzinc reagents has been recently published (**Scheme XXXII**).[103] Aminoalkylzinc reagents readily available *in situ* from corresponding aminoalkyl Grignard reagents, undergo cross-coupling reaction with various aryl and heteroaryl bromides, chlorides and triflates under optimized conditions [$Ni(acac)_2$ (2.5 mol %),

[103] Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529-5532.

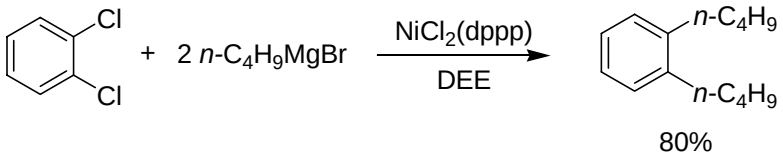
bis-(2-diphenylphosphinophenyl)ether (5 mol %)(DPE-Phos) and THF-NMP (9:1) at 25 ^{o}C] gave the best results.



Scheme XXXII

Other kind of electrophiles different from organic halides, carboxylic acid derivatives such as anhydrides, fluorides and chlorides, have been recently shown to react with diorganozinc reagents and organozinc halides in the presence of Ni catalysts.[104]

Tamao reported a Ni-catalyzed cross-coupling of aryl halides with alkyl Grignard reagents. The catalytic activity significantly depended on the nature of the phosphine ligands and the following order is generally observed: $Ni(dppp)Cl_2$ > $Ni(dppe)Cl_2$ > $Ni(PR_3)_2Cl_2$ > $Ni(dppb)Cl_2$.[105] Even alkyl-Grignard reagents containing *β*-hydrogen atom(s) can selectively undergo the cross-coupling reaction, as exemplified by the synthesis of *o*-dibutylbenzene (**Scheme XXXIII**).



Scheme XXXIII

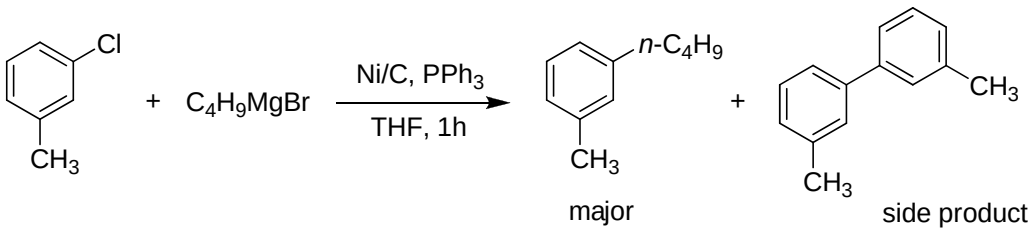
Simpler procedures for utilizing Ni/C as a 'heterogeneous' catalyst in Kumada couplings have also been developed (**Scheme XXXIV**).[106] Since Ni/C serves as a

[104] (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174-175. (b) Johnson, J. B.; Yu, R. T.; Fink, P.; Bercot, E. A.; Rovis, T. *Org. Lett.* **2006**, *8*, 4307-4310. (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247-254.

[105] (a) Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23-26. (b) Kumada, M.; Tamao, K.; Sumitani, K. *Org. Synth.* **1978**, *58*, 127-133.

[106] Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190-1199.

reservoir for the active Ni(0) species actually involved in the catalytic cycle in solution, the use of Ni(II) and its prior reduciton with *n*-BuLi is no longer required.



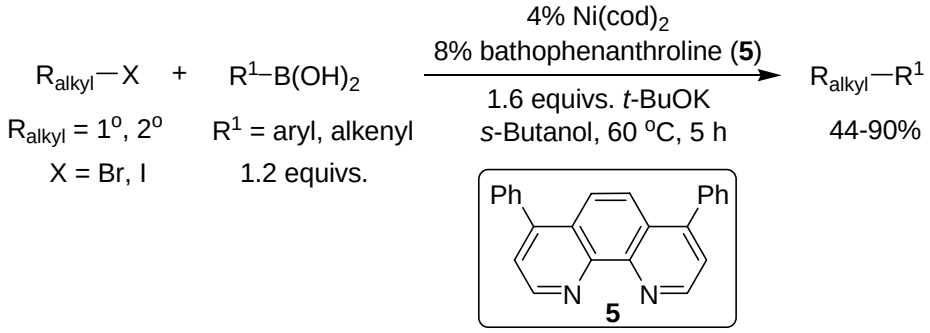
Scheme XXXIV

II.d. C(sp^2)–C(sp^3) bond formation: coupling of C(sp^3) electrophiles

As previously mentioned, the alternative coupling of an alkyl halide with an aryl or alkenylmetal reagent to form C(sp^2)–C(sp^3) bonds has been traditionally disregarded due to the potential β-elimination of hydrogen on the intermediate alkylmetal complexes. This limitation can be overcome by the use of promoters, like 4-(trifluoromethyl)styrene, 4-fluorostyrene, etc., or additives, like dienes, which facilitate the reductive elimination from the diorganonickel complex.

The use of alkyl electrophiles as coupling partners markedly increases the exceptional utility of cross coupling reactions. A variety of transition metals, such as palladium, nickel, iron, cobalt, and copper, mediate the ready coupling of a wide range of primary alkyl halides with organometallic reagents containing boron, silicon, tin, zinc, and magnesium. In contrast, the cross-coupling of secondary alkyl halides remains a challenging task. The added steric hindrance of a secondary alkyl halide increases the energy barrier to oxidative addition and thus makes traditional transition-metal-catalyzed processes much more difficult. Nevertheless, there has been a dramatic rise in the development of cross-coupling reactions of secondary alkyl halides, particularly in the last five years. The development of these new methodologies is significantly expanding the scope of transition-metal-catalyzed processes. Recent studies have investigated the stereochemical outcome of cross-coupling reactions and given insight into the reaction mechanisms. Asymmetric processes with racemic starting materials have also been developed.

Zhou and Fu developed the first Suzuki coupling of unactivated primary and secondary alkyl bromides and iodides in 2004.[107] The cross-coupling was carried out with $Ni(cod)_2$ and the bidentate pyridine ligand, bathophenanthroline (**Scheme XXXV**). Other metals, such as palladium, displayed no activity. A range of cyclic and acyclic secondary alkyl bromides and iodides were coupled with substituted aryl, heteroaryl, and alkenyl boronic acids. Primary, tertiary, and functionalized alkyl bromides, alkyl chlorides, alkyl boronic acids, and ortho-substituted aryl boronic acids could not be used as substrates under the specified conditions.



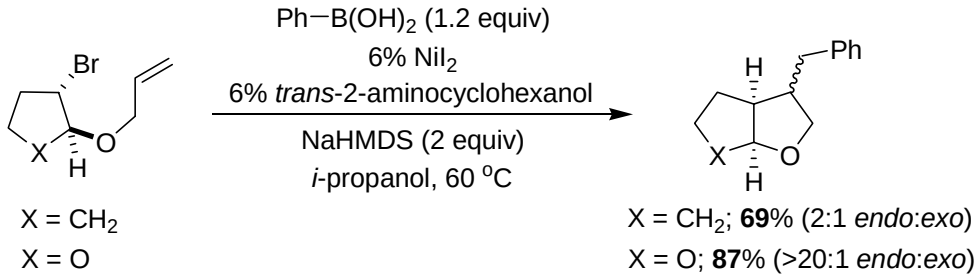
Scheme XXXV

In continuation, Fu and coworkers have reported that NiI_2/*trans*-2-aminocyclohexanol furnishes an active catalyst for Suzuki couplings of unactivated secondary alkyl halides (including challenging alkyl chlorides) with arylboronic acids.[108] Both the nickel precatalyst and the amino alcohols (prolinol and *trans*-2-aminocyclohexanol) are commercially available and air-stable (versus air-sensitive $Ni(cod)_2$).

With alkyl bromides bearing a pendant olefin a cyclization/cross coupling sequence can be achieved under same standard conditions (**Scheme XXXVI**).

[107] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341.

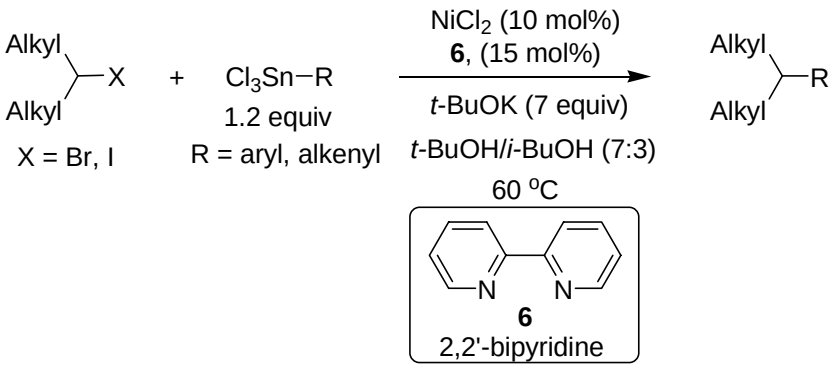
[108] González-Bobes, F; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360-5361.



Scheme XXXVI

Fu and coworkers have devoted a considerable effort to expanding the scope of palladium and nickel-catalyzed coupling reactions including unactivated *β*-hydrogen-containing alkyl halides as partners.[109] A particularly synthetically useful objective, although challenging due to slow oxidative addition and facile *β*-hydride elimination, is the cross-coupling of *secondary* alkyl halides.

So, they established a $NiCl_2$/2,2'-bipyridine catalyzed Stille cross-coupling reaction of secondary (as well as primary) alkyl halides with mono-organotin (aryl and alkenyl) reagents (**Scheme XXXVII**).[110,111] The advantage of this coupling is the ready availability of aryl- and alkenyltrichlorotin reagents ($RSnCl_3$) by redistribution of commercially available aryl- and alkenyltributylstannanes with $SnCl_4$.



Scheme XXXVII

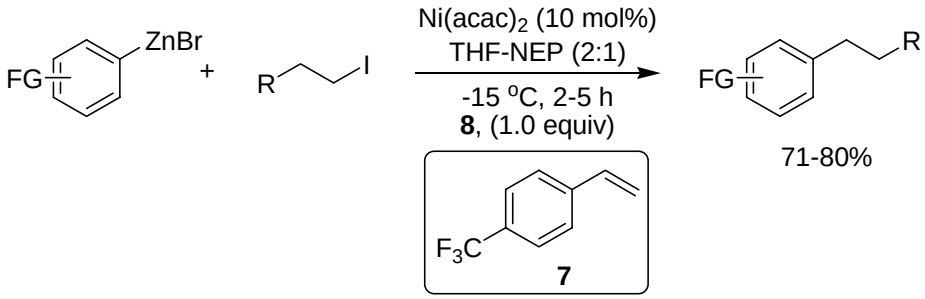
In particular and with relation to the use of organozinc derivatives as nucleophiles, Knochel and co-workers developed, in 1998, a new powerful Ni-catalysed

[109] Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525-1532.

[110] Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510-511.

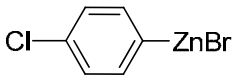
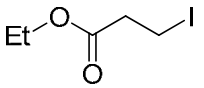
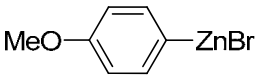
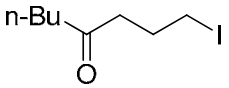
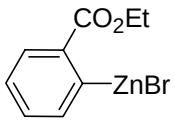
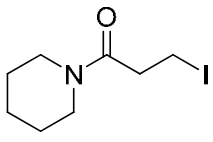
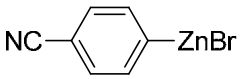
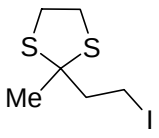
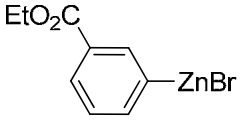
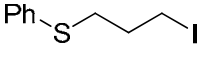
[111] Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3962-3965.

cross-coupling reaction of arylzinc bromides with various polyfunctional alkyl iodides in the presence of $Ni(acac)_2$ (10 mol %) and 4-(trifluoromethyl)styrene in THF:NMP (2:1), which produces highly functionalised cross-coupling products in good yields (**Scheme XXXVIII**).[112] 4-(Trifluoromethyl)styrene (**7**) is supposed to facilitate the reductive elimination from the intermediate R^1-Ni-R^2 complex over the potentially competing β–hydride elimination by removing electron density from the metal centre.



Scheme XXXVIII

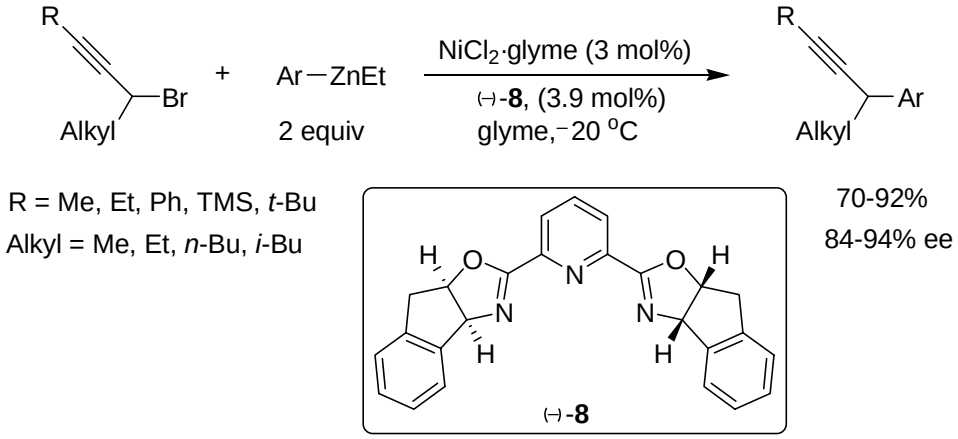
Table 4. *Ni(II)-catalysed cross-coupling of arylzinc bromides with primary alkyl iodides in the presence of 4-(trifluromethyl)styrene*

Entry	Arylzinc bromide	Alkyl Iodide	Yield (%)
1			71
2			72
3			72
4			80
5			75

[112] Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186-11187.

As illustrated in **Table 4**, both electron-rich and electron-poor arylzinc species are suitable cross coupling partners. The catalyst displays good functional group compatibility, effecting coupling in the presence of esters (entries 1, 3, and 5), aryl chlorides (entry 1), ketones (entry 2), tertiary amides (entry 3), nitriles (entry 4), 1-3-dithianes (entry 4), and thioethers (entry 5).

Fu and coworkers have developed a stereoconvergent method for the catalytic asymmetric Negishi cross-coupling of racemic secondary propargylic halides with arylzinc reagents.[113] No compound of this family of halides had previously been described as a suitable partner in such coupling processes. From a practical point of view, it is noteworthy that the catalyst components ($NiCl_2$·glyme and pybox ligand **8**) are commercially available. This stereoconvergent method can be employed for asymmetric Negishi couplings of alkyl and aryl-substituted propargylic bromides, the alkyl substituent can range in size from methyl to *t*-butyl (**Scheme XXXIX)**. C–C bond formation proceeds in generally good yield and enantioselectivity with an array of functionalized arylzinc reagents, including compounds that contain heterocycles.



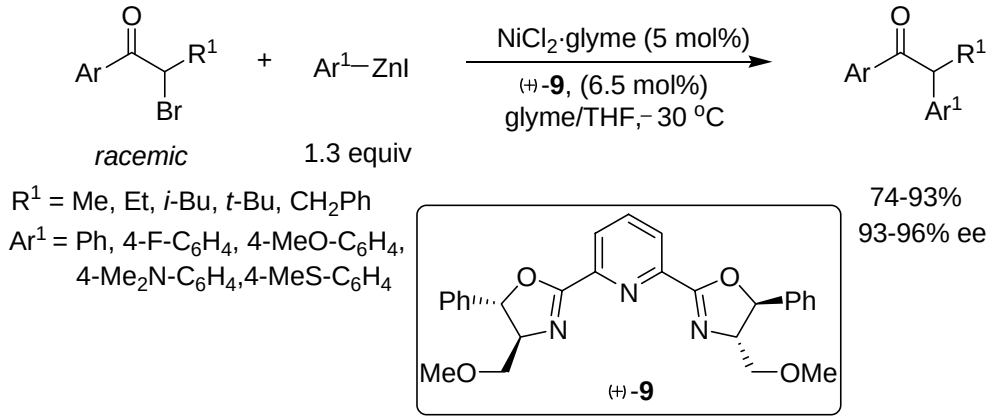
Scheme XXXIX

Recently, Fu has developed the first catalytic asymmetric method for cross-coupling arylzinc reagents with α-haloketones, specifically, the $NiCl_2$·glyme/**9**-catalyzed reaction of arylzincs with racemic secondary α-bromoketones (**Scheme XL**).[114] This stereoconvergent C–C bond forming process occurs under unusually mild

[113] Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645-12647.

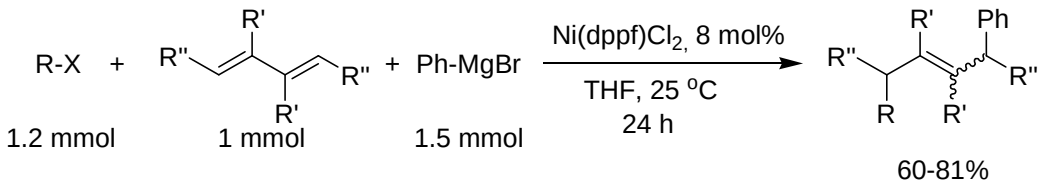
[114] Lundin, P. M.; Esquivias, J.; Fu, G. C. *J. Angew. Chem. Int. Ed.* **2009**, *48*, 154-156.

conditions (−30 °C and no activators), thereby allowing the generation of potentially labile tertiary stereocenters.



Scheme XL

On the other hand, coupling of aryl Grignard reagents to alkyl halides has also been scarce, mainly because the *β*-elimination of hydrogen on the intermediate alkylmetal complexes precludes the reaction. However, in 2004, Kambe and coworkers developed a new method for the regioselective three component cross-coupling reaction of alkyl halides, 1,3-butadienes, and aryl-Grignard reagents by the use of a nickel catalyst.[115] This reaction proceeds efficiently at 25 °C using Ni(dppf)Cl_2 as a catalyst (**Scheme XLI**). Alkyl chlorides, bromides, and iodides can be used as suitable alkylating reagents. The reaction also proceeds when arylzinc halides are used instead of Grignard reagents.



Scheme XLI

[115] Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 905-908.

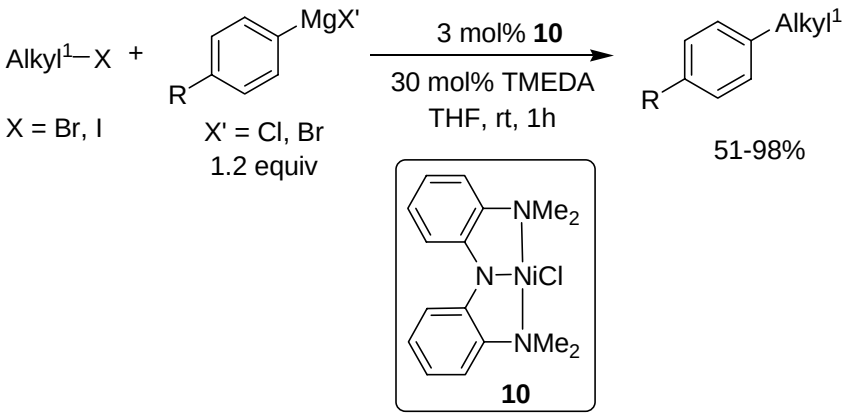
Competitive reactions of a mixture of primary, secondary, and tertiary alkyl bromides showed that the reactivities of the halides increased in the order primary<secondary<tertiary (**Table 5**).

Table 5. *Ni-catalyzed three component coupling reaction*[a]

Entry	R-X	R'	R''	Isolated Yield (%)	*E/Z*[b]
1	*n*-Bu-Br	Me	H	69	59/41
2	*i*-Pr-Br	Me	H	91	67/33
3	*t*-Bu-Br	Me	H	74	56/44
4	*c*-Hex-Br	Ph	H	73	79/21
5	*c*-Hex-Br	H	Ph	60	100/0
6	*s*-Bu-Cl	Me	H	63	57/43
7	*t*-Bu-Cl	Me	H	81	52/48

[a]Phenyl magnesium bromide is used as the nucleophile for all entries. [b]Determined by GC.

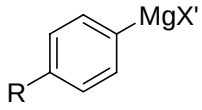
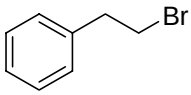
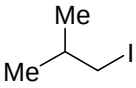
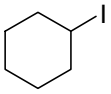
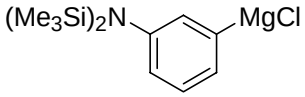
Besides, very recently, Hu and coworkers have explored the applications of a stable, and easy to handle, Ni^{II} pincer complex **10** that catalyzes efficiently the $C(sp^3)$–$C(sp^2)$ Kumada-Corriu-Tamao coupling of nonactivated and *β*-H containing alkyl halides with aryl and heteroaryl Grignard reagents.[116] The reaction demands only a relatively low loading of catalyst (3 mol %) and is completed within a short period of time (1 h). Primary iodides and bromides and certain secondary iodides can be coupled in high yields (**Scheme XLII, Table 6**).



Scheme XLII

[116] Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756-9766.

Table 6. *Kumada-Corriu-Tamao coupling of alkyl halides with aryl Grignard reagents*

Entry	Alkyl[1]-X		Yield (%)[a]
1	Octyl-Br	R = H, CH_3, OCH_3, NMe_2	67-87
2	Octyl-I	R = H, F, OCH_3	80-98
3		R = H, F, OCH_3	78-90
4		R = H, F, OCH_3	72-86
5	*n*-Bu-I	R = CH_3, OCH_3, NMe_2	85-99
6		R = H, F	51-62
7	Octyl-I, *sec*-Bu-I, *c*-Hex-I, etc.		92-99[b]

[a]GC yield. [b]Amine was formed after workup.

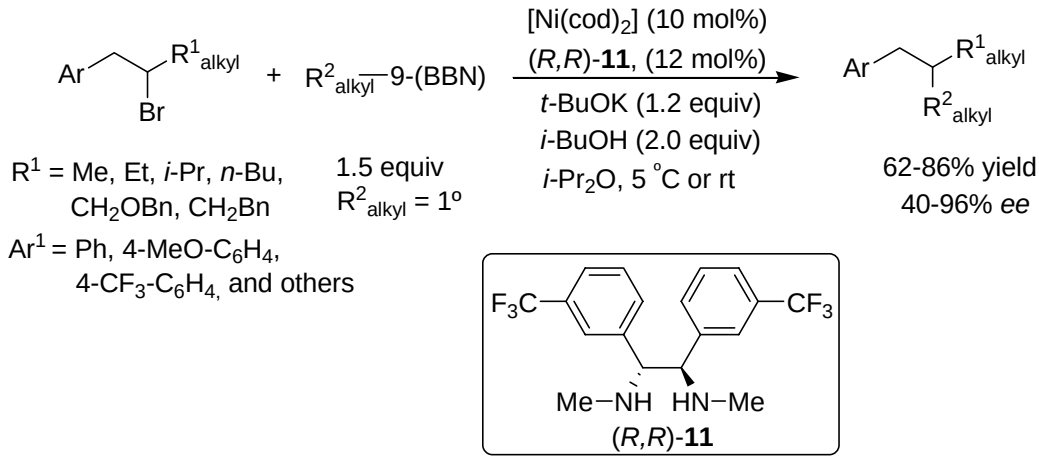
Due to the mild conditions employed, the reactions tolerate a wide range of sensitive functional groups. Alkyl halides containing ester, amide, nitrile, ether, thioether, acetal, alcohol, indole, pyrrole, furan, pyrazole and *N*-Boc groups are selectively coupled. Furthermore, functionalized aryl and heteroaryl Grignard reagents, including those of the Knochel-type, could be coupled to nonactivated alkyl halides for the first time. With the demonstration of efficient coupling between functionalized alkyl halides and functionalized Grignard reagents, the work expands significantly the scope of Kumada-Corriu-Tamao coupling, making this atom-economic and cost-effective cross-coupling technology attractive for the construction of more complex molecules and materials.

IIe. C(sp^3)–C(sp^3) bond formation

As it has been stated above, palladium- or nickel-catalyzed cross-coupling of alkyl electrophiles appeared to be strongly discouraged. Recently, however, a number of studies have clearly demonstrated that these potential problems are in fact surmountable.

Suzuki[32] established the first examples of palladium- or nickel-catalyzed cross-couplings of unactivated, *β*-hydrogen-containing alkyl electrophiles. Specifically, $Pd(PPh_3)_4$ catalyzed couplings of primary alkyl iodides with 9-alkyl-9-BBN reagents.

Fu and coworkers demonstrated that Ni/*trans-N,N'*-dimethyl−1,2-cyclohexanediamine affords the first method for achieving a range of alkyl–alkyl Suzuki reactions of unactivated secondary alkyl halides with alkylboranes.[117] In continuation they developed the first effective method for asymmetric cross-couplings of *unactivated* alkyl electrophiles, specifically, a nickel-based catalyst for stereoconvergent Suzuki reactions of homobenzylic bromides with alkylboranes.[118] Ligand **11** was found to provide the most selective catalyst (**Scheme XLIII**).



Scheme XLIII

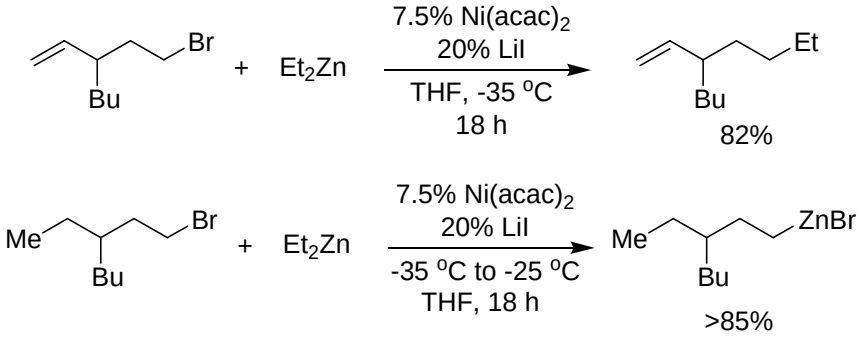
During studies of radical cyclizations using Et_2Zn, Knochel discovered that $Ni(acac)_2$/LiI serves as an efficient catalyst for $C(sp^3)-C(sp^3)$ bond formation (**Scheme XLIV**, top).[119] A control experiment that employed the saturated analogue of the alkyl halide resulted only in Br-Zn exchange (**Scheme XLIV**, bottom), thereby implicating the remote C=C double bond as a critical element for this new cross-coupling process.

[32] Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691-694.

[117] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603.

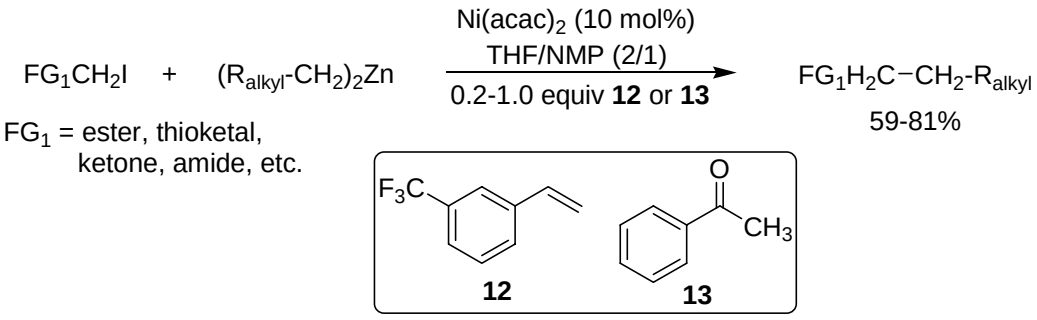
[118] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694-6695.

[119] Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1996**, *34*, 2723-2725.



Scheme XLIV

Knochel and co-workers pioneered the development of Ni-catalysed alkyl–alkyl Negishi cross-coupling reaction between polyfunctional primary iodoalkanes and primary diorganozinc compounds in the presence of a promoter.[120] *m*-Trifluoromethylstyrene (**12**) or acetophenone (**13**) promoted the reaction allowing efficient and fast coupling at varying temperatures from −78 to −35 °C in THF/NMP (1-methyl-2-pyrrolidinone) (**Scheme XLV**). Iodoalkanes containing functional groups like ester, amide, keto, and thioketal coupled smoothly, demonstrating the functional group tolerance of this cross-coupling reaction.

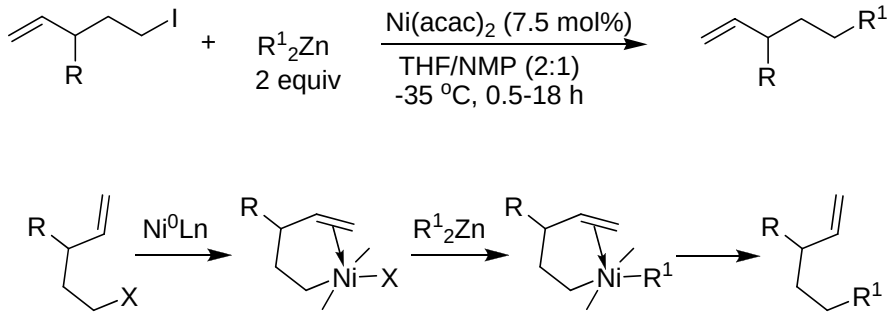


Scheme XLV

The key for the success of this reaction was suggested to be the formation of intermediate Ni(II)-olefin complexes, which further underwent easy transmetalation and reductive elimination reactions.

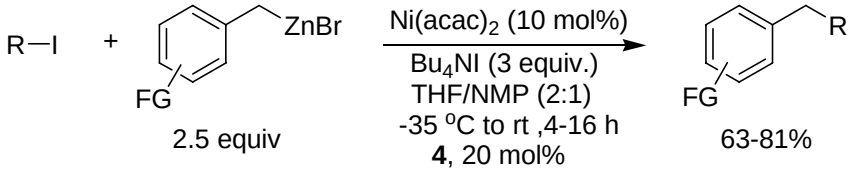
[120] Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544-3553.

The presence of the unsaturation (double bond, carbonyl group, cyano group) in an alkyl halide facilitated its coupling with functionalised diorganozincs in the presence of $Ni(acac)_2$ catalyst, leading to a broad range of polyfunctional cross-coupling products in good to excellent yields (**Scheme XLVI**).[121]



Scheme XLVI

The addition of Bu_4NI (3 equiv) and *p*-fluorostyrene (**4**) as promoter (0.2 equiv) greately enhanced reaction efficiency.[122] It allowed a new and efficient Ni(0)-catalysed cross-coupling between primary alkyl iodides and benzylzinc bromides leading to the desired $C(sp^3)–C(sp^3)$ coupling product (**Scheme XLVII**).



Scheme XLVII

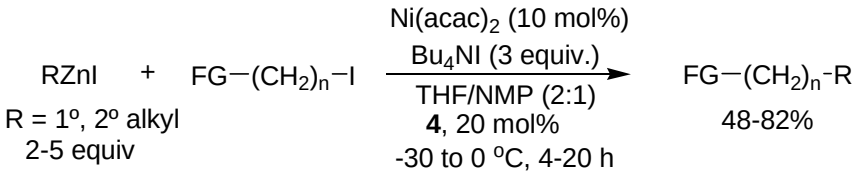
In a subsequent paper, Knochel established that unreactive primary and secondary alkylzinc iodides also underwent nickel-catalysed cross-coupling with functionalised alkyl iodides (**Scheme XLVIII**).[123] *p*-Fluorostyrene (**4**) facilitated the reductive elimination of the Ni(II) complex by removing electron density from the metal center. The effect of Bu_4NI was less clear, although an excess of ammonium salt was

[121] Giovannini, R.; Stüdemnann, N.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390.

[122] Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323-1326.

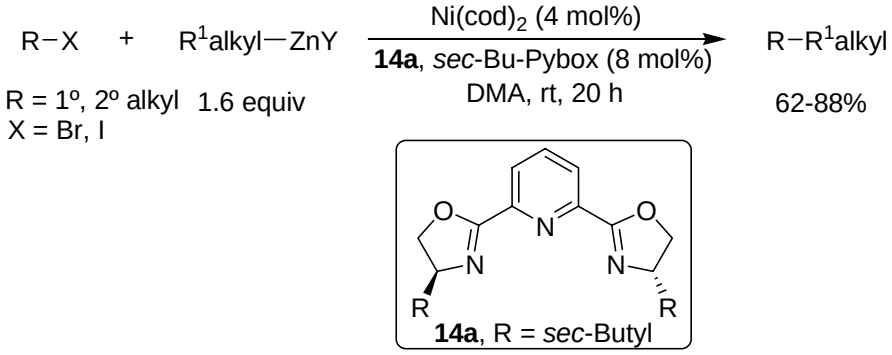
[123] Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79-85.

necessary to achieve rate enhancent. It has been suggested that coordination of iodide to the organozinc halide may lead to 'zincate' type of intermediate, which may be a more reactive transmetalating species. Other possibilities are change of the ionic strength of the medium or stabilization of highly reactive low-valent nickel species.



Scheme XLVIII

In 2003, Fu reported that the catalytic system $Ni(cod)_2$ (cod: 1,5-cyclooctadiene)/(4%)/(*sec*-Bu)-Pybox (8%), in DMA (*N*,*N*-dimethylacetamide), catalyzed the room temperature cross-coupling of a range of secondary and primary alkyl bromides and iodides with alkylzinc halide in moderate to good yield (**Scheme XLIX**).[124]

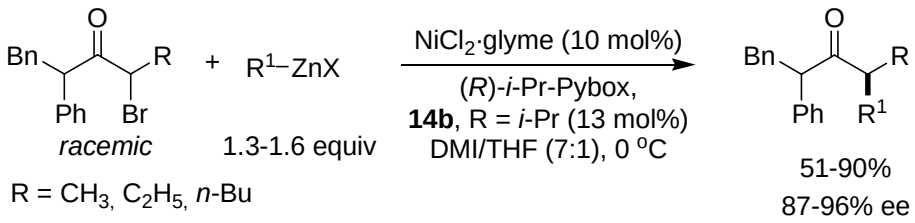


Scheme XLIX

This group has reported several articles in which the scope of Ni-catalyzed alkyl–alkyl bond formation has been significantly broadened. Asymmetric Ni/(*i*-Pr)-Pybox-catalysed Negishi cross-coupling of secondary α-bromoamides with an array of functionalised and unfunctionalised organozinc reagents has been shown to proceed in

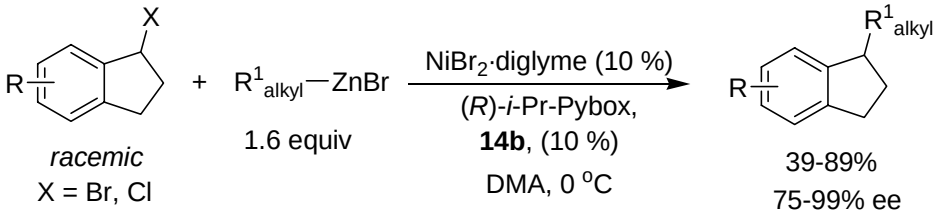
[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

good yield and with high enantioselectivity (**Scheme L**; DMI=1,3-dimethyl-2-imidazolidinone).[125]



Scheme L

Fu and coworkers has described the first highly enantioselective cross-coupling of secondary benzylic halides with organozinc reagents. Specifically, Negishi reactions of racemic bromides and chlorides with organozinc reagents (**Scheme LI**).[126]



Scheme LI

Interestingly, Ni-catalyzed Negishi coupling of alkyl halides with alkyl nucleophiles seems to follow a very different mechanism. As in the previous cases, isolation of intermediates and study of their reactivity has been the key to understand the process. Computational studies have also provided valuable information. Although mechanistic studies are scarce, the main features of the reaction pathway for $C(sp^3)$–$C(sp^3)$ coupling involving terdentate nitrogen ligands have been established.

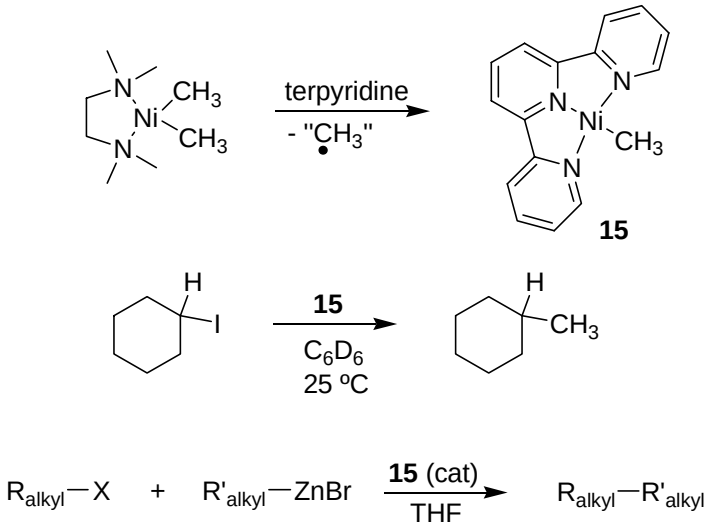
Especially important in this respect is the isolation of complex (terpyridyl)NiMe (**15**) by reaction of $(TMEDA)Ni(CH_3)_2$ (TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylene-diamine) with terpyridine (**Scheme LII**), in a process which is not well understood.[127] This paramagnetic metal complex is a rare example of Ni(I) organometallic species

[125] Fisher, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595.

[126] Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483.

[127] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100-8101.

stable at room temperature. It is capable of transferring its methyl group to iodocyclohexane to produce methylcyclohexane in high yield.



$$R_{alkyl}—X + R'_{alkyl}—ZnBr \xrightarrow[THF]{\textbf{15}\ (cat)} R_{alkyl}—R'_{alkyl}$$

Scheme LII

In addition, **15** shows catalytic activity in the cross-couplings of alkyl electrophiles performed under Negishi-like conditions. Although the precise mechanism of alkyl–alkyl Negishi cross-coupling is not fully understood, square-planar alkyl–nickel(I) complexes have been proposed as the active species.[128]

Both the magnetic susceptibility (μ_{eff} = 1.64 μ_B) and the redox potential (-1.32 v *vs* Ag/Ag^+ in THF solution) are fully consistent with a Ni(I) species, albeit the square-planar geometry is typical of Ni(II) derivatives. DFT studies of models of these complexes with terpyridine[129] as ligand have shed light on the actual structure of these complexes. The unpaired electron is localized in a singly-occupied molecular orbital (SOMO) which extends mainly on the terdentate ligand. In consequence, this complexes must be better considered as Ni(II) species coordinated to alkyl and to *anionic* terdentate ligand. This is fully consistent with the geometry and the magnetic properties of the complexes.

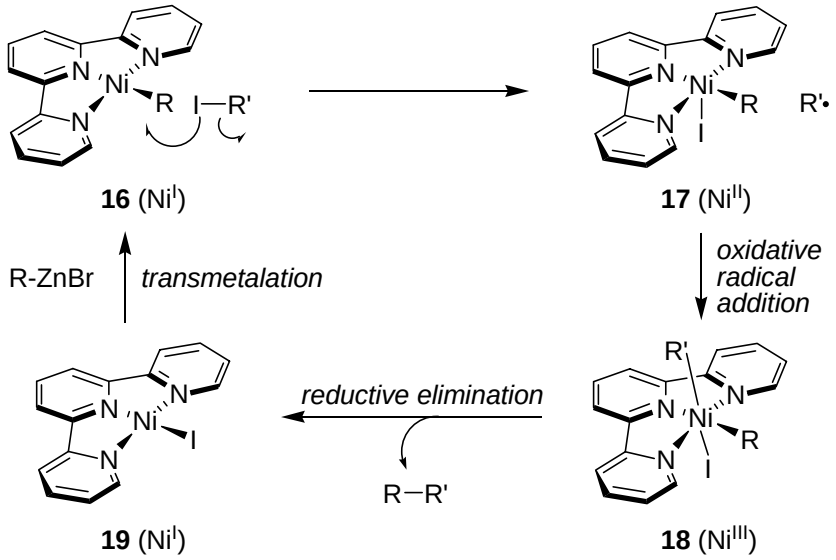
On the basis of computational and experimental results, Vicic proposed a mechanism (**Scheme LIII**) in which a (terpyridine)Ni-alkyl complex (**16**) similar to **15**,

[128] Ni(I) complexes containing phosphine ligands: Kitiachvili, K. D.; Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2004**, *126*, 10554-10555.

[129] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

formed by reaction of the precatalyst with RZnX, reacts with the alkyl halide to form an alkyl radical and a Ni(II) complex **17**. A recent computational study suggests that iodide is actually coordinated to Ni, which is different from the initial proposal. The alkyl radical in close proximity to the metal center would afford nickel(III)-dialkyl species **18** by oxidative radical addition. Fast reductive elimination of cross-coupled alkane then occurs to release electrons from the antibonding orbital of **18** leaving **19**, which would regenerate the active species by transmetalation with the alkylzinc halide.[130] This states that certain cross-coupling reactions of alkyl electrophiles with alkylzinc reagents seem to follow a radical pathway.

We calculated that oxidative addition of the alkyl halide to the Ni(I) complex to release an alkyl radical is a feasible process,[131] since it shows a low activation energy compatible with the room temperature conditions in which the cross-coupling takes place. Although both oxidative addition and transmetalation are calculated to be endoergic in the gas phase, the presence of solvent tends to favour these processes. Moreover, the reductive elimination step is exoergic enough and provides the driving force for the overall process.



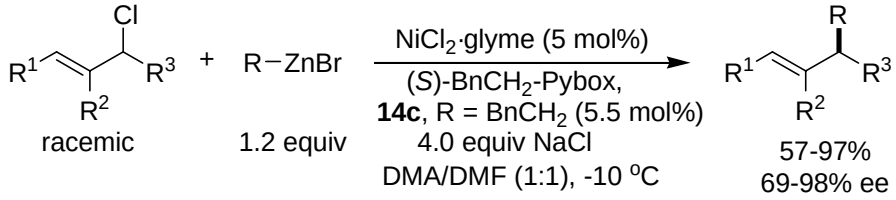
Scheme LIII

Shortly after, Fu reported a catalytic system for the regioselective asymmetric Negishi cross-coupling of racemic secondary allyl chlorides with readily available

[130] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680-3688.

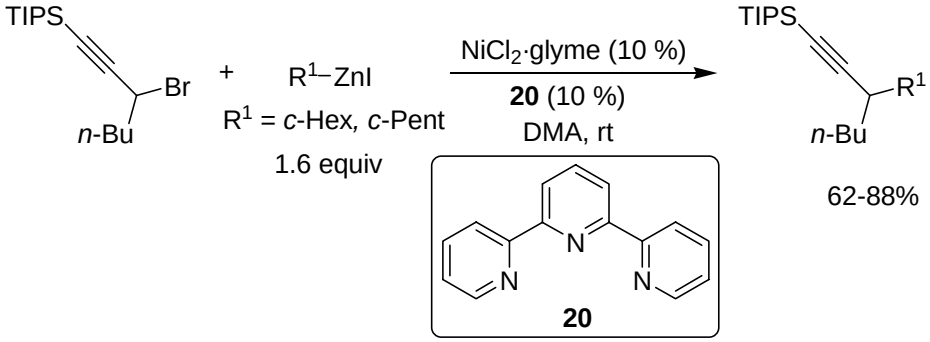
[131] Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.

organozinc halides.[132] Both symmetrical (R^1=R^3=CH_3) and unsymmetrical (R^3=CH_3 and R^1=CH_3, *n*-Pr, *i*-Pr) allyl chlorides couple in high yields and enantioselectivity. Moreover, the process is stereoconvergent: the two enantiomers of the racemic substrate are transformed into the same enantiomer of the product with good stereoselectivity (**Scheme LIV**).



Scheme LIV

Fu has also developed the first method for secondary–secondary alkyl cross-couplings with nickel-based system for coupling secondary propargylic halides with secondary alkylzinc reagents under mild conditions (at room temperature and with no basic activators) (**Scheme LV**).[133]



Scheme LV

On the other hand, Kambe and coworkers found that Ni catalyzes the cross-coupling reaction of alkyl chlorides, bromides, and tosylates with Grignard reagents in the presence of a 1,3-butadiene as an additive (**Scheme LVI**).[134] A catalytic cycle involving Ni(II) and Ni(IV) species has been proposed.

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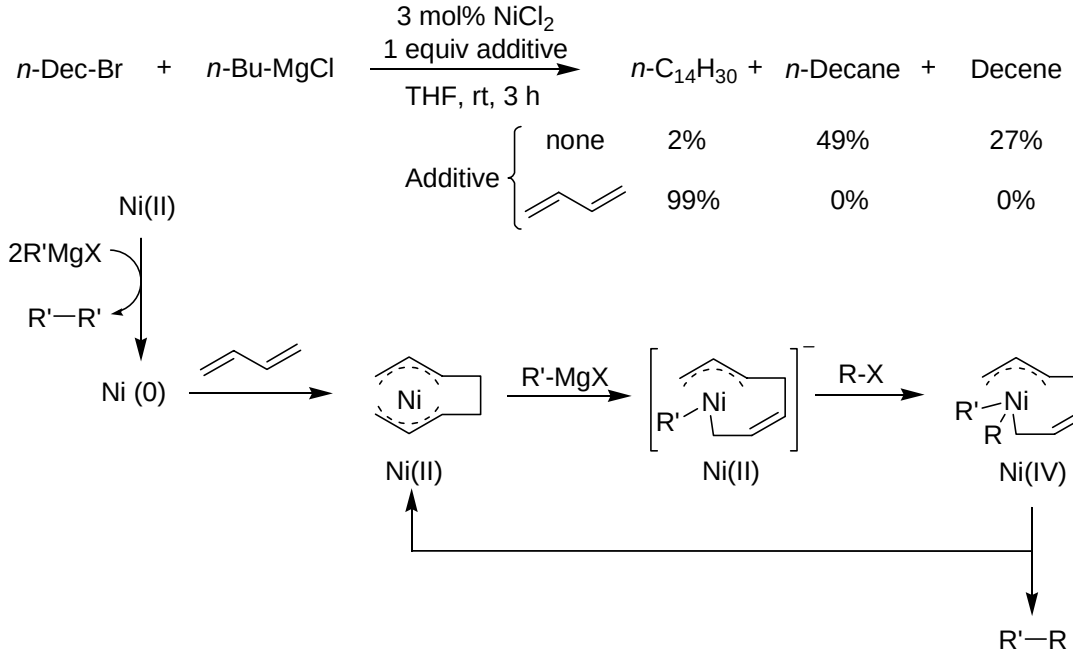
[132] Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756-2757.

[133] (a) Smith S. W.; Fu, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 9334-9336. (b) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211-4213.

[134] Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223.



Scheme LVI

This reaction proceeds efficiently by the use of primary and secondary alkyl- or arylmagnesium halides under mild conditions. The use of 1,3-butadiene as an additive instead of phosphine ligands is the key to attaining high yields of the cross-coupling products (**Table 7**).

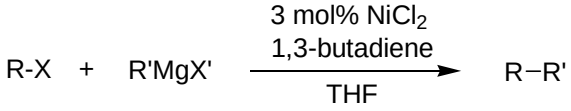
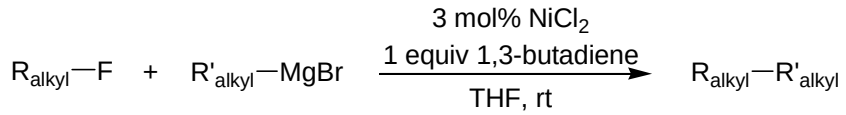


Table 7. *Kumada-Corriu-Tamao coupling of alkyl halides with alkylmagnesium halides*

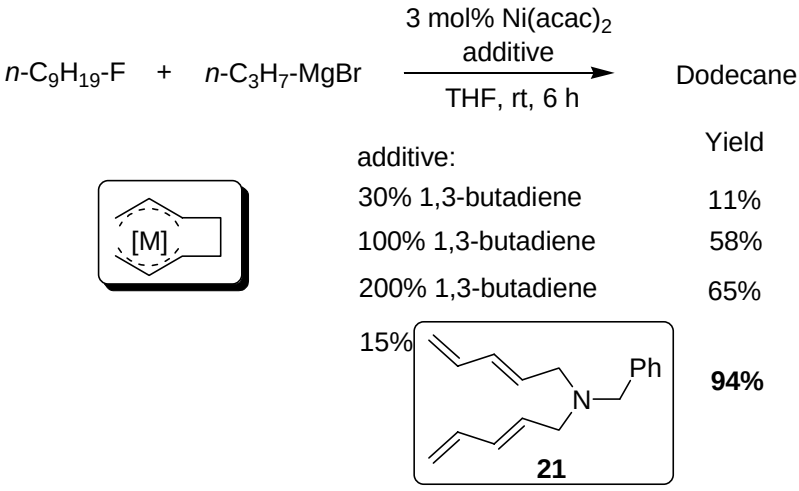
Entry	R-X	R'-MgX'	Yield (%)
1	*n*-$C_{10}H_{21}Br$	*n*-Bu-MgCl	100
2	(4-Br-C_6H_4)CH_2CH_2Br	*n*-Bu-MgCl	100
3	$PhCH_2CH_2OTs$	Et-MgBr	87
4	*n*-Bu-OTs	*n*-Bu-MgCl	100
5	*n*-Oct-Br	Ph-MgBr	90
5	*n*-Oct-Br	*i*-Pr-MgCl	72
6	*n*-Oct-Cl	*n*-Bu-MgCl	96

Kambe also revealed the first example of a metal-catalyzed cross-coupling reaction of alkyl fluorides with Grignard reagents. These reactions proceed efficiently between primary alkyl fluorides and various Grignard reagents under mild conditions in the presence of nickel salts (**Scheme LVII**).[135]



Scheme LVII

As an extension of this study, Kambe disclosed the first example of a nickel-catalyzed C–C bond forming reaction using nonactivated alkyl fluorides in the presence of tetraene **21** (**Scheme LVIII**).58[136]



Scheme LVIII

Tetraene **22** exerted dramatic effects that improved the cross-coupling reactions of organozinc reagents with alkyl halides catalyzed by nickel. This reaction proceeded efficiently by the use of primary and secondary alkyl or aryl zinc reagents under mild conditions (**Scheme LIX**).

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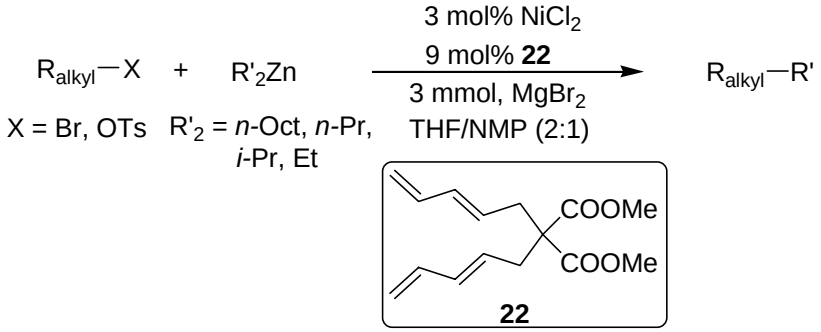
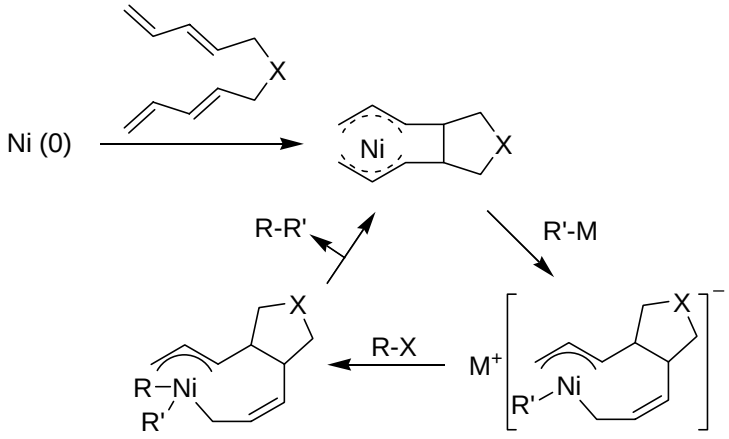
[135] Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646-5647.

[136] Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 6180-6182.



Scheme LIX

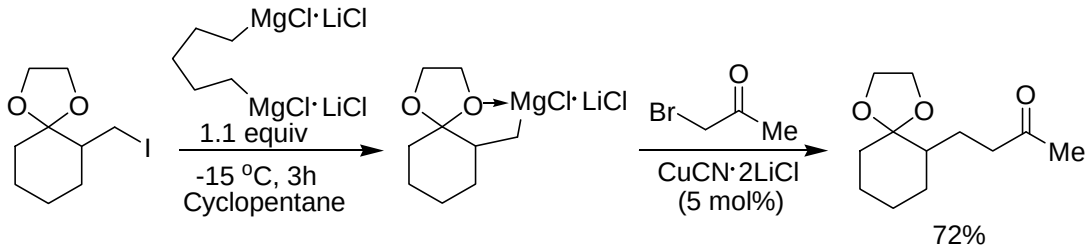
A plausible reaction pathway is shown in **Scheme LX**. A bis-π-allylnickel structure is constructed by the oxidative cycloaddition of Ni(0) with two butadiene moieties of a 1,3,8,10-tetraene (**22**). An organomagnesium or -zinc reagent attacks the bis-π-allyl complex to generate the η^1,η^3-octadienediylnickelate complex, which then reacts with alkyl halides to give a diorganonickel complex. Subsequent reductive elimination affords the coupling product along with bis-π-allylnickel to complete the catalytic cycle.



Scheme LX

Recently Knochel has reported that primary alkyl iodides bearing an acetal, a ketal, an ester, or a pyridine ring can be converted into organomagnesium derivatives by an I/Mg-exchange using *i*-Pr_2Mg·LiCl or $ClMg(CH_2)_5MgCl$·2LiCl. Quenching the

resulting sp^3-hybridized Grignard reagent with a range of alkyl electrophiles allows the preparation of various functionalized products under copper catalysis (**Scheme LXI**).[137]



Scheme LXI

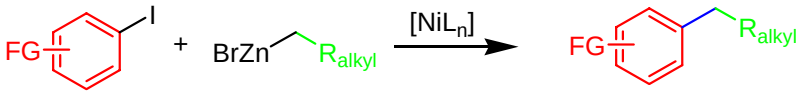
[137] Rauhut, C. B.; Vu, V. A.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2008**, *10*, 1187-1189.

OBJECTIVES

Objective 1.

Ni-catalyzed coupling reaction of organozinc nucleophiles with organic electrophiles shows a broad scope with respect to both coupling partners, and high functional group tolerance. Only a few examples of Ni-catalyzed Negishi cross-coupling reactions of $C(sp^2)$ electrophiles with alkylzinc reagents have been reported to date (*see section IIc of the Introduction*).

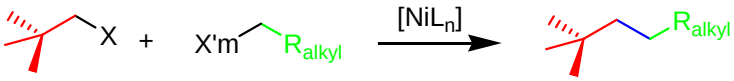
So initially our interest was focused on the development of Ni-catalyzed efficient Negishi cross-coupling reactions between $C(sp^2)$ electrophiles like aryl, heteroaryl or alkenyl halides with alkylzinc bromides under mild conditions.



Objective 2.

Cross-coupling reactions leading to $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp)$ bonds have been extensively exploited. In contrast the formation of $C(sp^3)$–$C(sp^3)$ bonds in the presence of functional groups has remained elusive for years.

So our second objective was to develope nickel catalyzed Negishi and Kumada type cross-coupling reaction of alkyl partners in order to afford $C(sp^3)$–$C(sp^3)$ bonds.

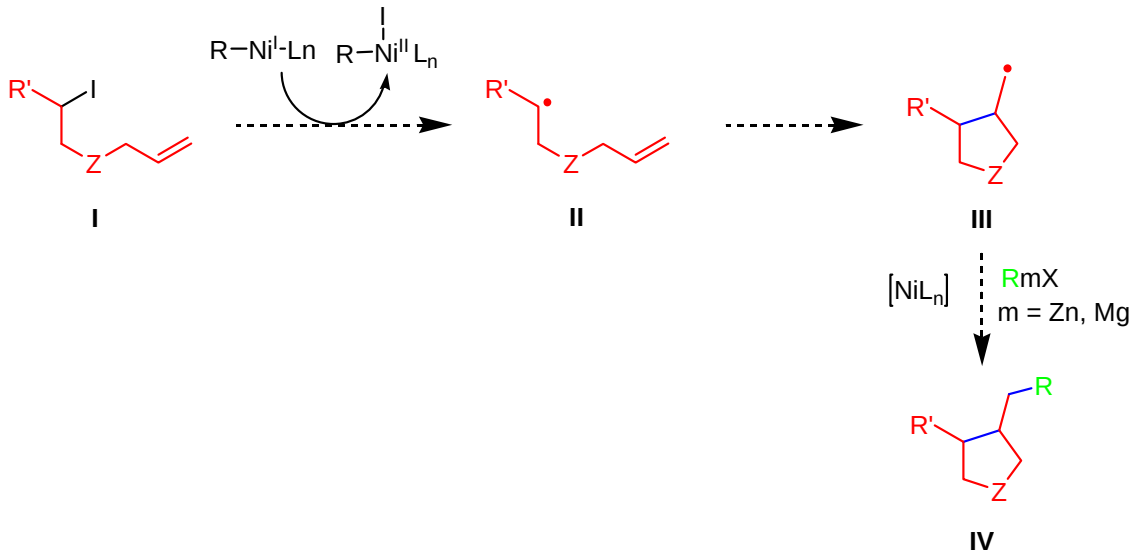


X = Cl, Br, I

m = Zn, Mg; X' = Cl, Br

Objective 3.

On the basis of the previously mentioned precedents, we intended to develop a Ni-catalyzed cyclization of alkyl halides containing an alkene group, to give two $C(sp^3)$–$C(sp^3)$ bonds in a single operation.



I II III IV

Scheme: Ni-catalyzed cyclization and cross-coupling reaction.

We tried to take advantage of the formation of radicals by reaction of Ni(I) complexes with alkyl iodides, and the intramolecular cyclization ability of these radicals with alkenes. Once the cyclized compound had been formed, coupling with alkylzinc or alkyl magnesium halides would afford the final products.

We also liked to study the stereochemistry and mechanistic aspects of this cascade cyclization/cross-coupling reaction on the basis of experimental and computational studies

RESULTS AND DISCUSSION

I. Nickel-catalyzed cross-coupling reaction of C(sp^2) electrophiles with alkylzinc bromides

C–C coupling reactions are among the most important transformations in organic synthesis, as they make it possible to build up complex structures from readily available components in diverse ways. As a result of the development of a large number of metal-catalyzed coupling reactions of various C–X-containing compounds (X = Cl, Br, I, OTf, OMs, N_2^+, etc.; Tf = trifluoromethanesulfonyl, Ms = methanesulfonyl) over the last three decades, efficient methods are now available for the direct formation of bonds between of sp^3-, sp^2-, and sp-hybridized carbon atoms.[1]

Not all C–C coupling reactions have been thoroughly examined and developed. The extensively used reactions with aryl or alkenyl electrophiles play a prominent role in organic synthesis because of the ready availability of substrates, their general applicability, their high selectivities, and the comparatively simple oxidative addition, and *β*-hydride elimination. The relatively mild reaction conditions of such processes, as well as the high tolerance of functional groups under palladium, nickel, and copper catalysis, contributed substantially to the advancement of these reactions.

Among all, Negishi cross-coupling reactions with organozinc reagents, constitute a valuable tool for the construction of C–C bonds. Due to excellent functional group tolerance, high chemoselectivity and excellent stereoselectivity of organozinc reagents in many reactions, organozinc compounds constitute ideal organometallic reagents for the construction of complex polyfunctional molecules. A large number of organozinc reagents are available commercially as standardized solutions in THF or can be prepared easily from organic halides and a highly reactive grade of metallic zinc ("Rieke zinc"),[138] which is likewise commercially available. Thus combined use of Zn nucleophiles and Ni catalysts is highly convenient for economical and environmental reasons as well, compared with other widely used coupling processes such as the Stille reaction.[139] Only a few examples of Ni-catalyzed Negishi reactions of aryl electrophiles

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[1] (a) *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, 1998. (b) *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, 2004.

[138] Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445-1453.

[139] Recent review on Ni-catalyzed Negishi Cross-Coupling Reactions: Phapale, V. B.; Cárdenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598-1607.

for the formation of $C(sp^2)$–$C(sp^3)$ bonds have been published to date (See *section* ***IIc.*** of the *Introduction* for a detailed discussion of Ni-catalyzed cross-coupling of $C(sp^2)$ electrophiles with alkylzinc reagents).[67]

Considering the widespread existence of $C(sp^3)$–$C(sp^2)$ bonds in natural products, medicinal compounds, and materials, further exploration of the Negishi coupling of alkyl zinc reagents, especially secondary alkyl zinc reagents bearing β-hydrogen atoms,[140] to achieve highly productive coupling is of great importance.

Our intention was to develope a Ni-catalyzed cross-coupling reaction which resulted in the formation of $C(sp^2)$–$C(sp^3)$ bonds, using $C(sp^2)$ electrophiles such as aryl, heteroaryl and alkenyl halides. Most of them are commercially available or easy to synthesize. In this way we have developed cross-coupling reactions of alkylzinc bromides with $C(sp^2)$ electrophiles in the presence of a wide variety of functional groups under mild conditions, and have proposed a reaction pathway based on computational results. The alternative use of alkyl electrophiles and arylzinc reagents has been traditionally disregarded due to the potential β-elimination of hydrogen on the intermediate alkylmetal complexes,[25a,27] although some examples have been reported.[112]

We have studied the reaction between *p*-iodoanisol (**1a**) and alkylzinc halide **2a** as a model to optimize the catalytic system. The air and moisture stable complex $[Ni(py)_4Cl_2]$[141] afforded the best results in the presence of bipyridine[142] (**Table 1**, entry 8). In addition, it should be noted that the reaction performed with 3% of catalyst loading, reaction completes with same efficiency with slight higher reaction time as compared with the reaction with 10% catalyst loading (**Table 1**, entry 7 *vs* 8).

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[67] Recent reports on Pd-catalyzed coupling of aryl halides and alkylzinc halides: (a) Bartrum, H. E.; Adams, H.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 3701-3712. (b) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923-3925. (c) Liu, Q.; Duan, H.; Luo, X.; Tang, Y.; Li, G.; Huang, R.; Lei, A. *Adv. Synt. Cat.* **2008**, *350*, 1349-1354. (d) Wang, H.; Liu, J.; Deng, Y.; Min, T.; Yu, G.; Wu, X.; Yang, Z.; Lei, A. *Chem. Eur. J.* **2009**, *15*, 1499-1507. (e) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532-7533.

[140] Luh, T.; Leung, M; Wang, K. *Chem. Rev.* **2000**, *100*, 3187-3204.

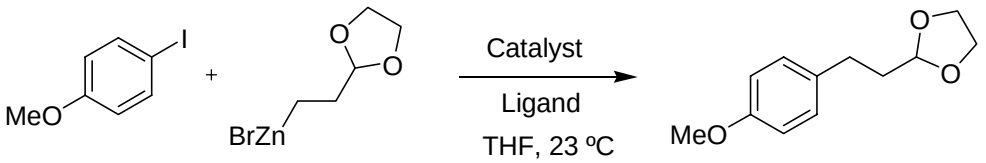
[25a] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3018-3020.

[27] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

[112] Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186-11187.

[141] (a) Long, G. J.; Clarke, P. J. *Inorg. Chem.* **1978**, *17*, 1394-1401. (b) Bachman, R. E.; Whitmire, K. H.; Mandal, S.; Bharadwaj, P. K. *Acta. Crystallogr. Sect. C* **1992**, *48*, 1836-1837.

[142] 2,2'-Bipyridine; Commercially available, Sigma-Aldrich (D216305).

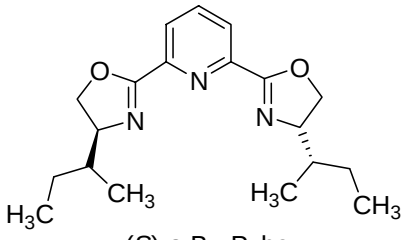


1a **2a** (2 equiv.) **3a**

Table 1. *Optimization of the conditions for aryl–alkyl cross-coupling reactions*

Entry	Catalyst (mol%)	Ligand (mol%)	t (h)	Yield (%)[a]
1	$Ni(cod)_2$ (10%)	bpy (10%)	2	43
2	$Ni(cod)_2$ (10%)	tpy (10%)	2	55
3	$Ni(cod)_2$ (10%)	(*S*)-*s*-Bu-Pybox (10%)	2	58
4	$Ni(py)_4Cl_2$ (5%)	PPh_3 (10%)	7	54
5	$Ni(py)_4Cl_2$ (3%)	PPh_3 (10%)	7	48
6	$Ni(PPh_3)_2Cl_2$ (3%)	PPh_3 (10%)	18	39
7	$Ni(py)_4Cl_2$ (10%)	bpy (10%)	2	80
8	**$Ni(py)_4Cl_2$ (3%)**	**bpy (3%)**	**3.5**	**80**
9	$Ni(py)_4Cl_2$ (10%)	tpy (10%)	2	61
10	$Ni(py)_4Cl_2$ (10%)	(*S*)-*s*-Bu-Pybox (10%)	2	67
11	$Ni(py)_4Cl_2$ (0.3%)	(*S*)-*s*-Bu-Pybox (0.3%)	8	80
12	$Ni(py)_4Cl_2$ (0.03%)	(*S*)-*s*-Bu-Pybox (0.03%)	24	48[b]

[a]Isolated yield. [b]Reaction is incomplete, ~40% starting material is recovered.



(*S*)-*s*-Bu-Pybox

In contrast to the previously reported couplings of alkyl electrophiles, terdentate nitrogen ligands (pybox ligands) were not so effective.[124] The use of $Ni(cod)_2$ (cod: 1,5-cyclooctadiene) and $Ni(PPh_3)_2Cl_2$ was less convenient either and gave low yields. The homocoupled compound derived from the alkyl zinc bromide was isolated in approximately 6% yield (relative to the starting nucleophile, 2 equiv) in most cases. The use of lower amounts of the nucleophile led to lower yield of cross-coupling products.

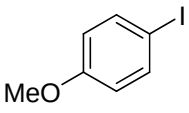
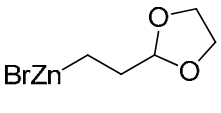
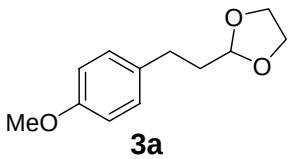
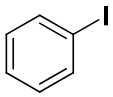
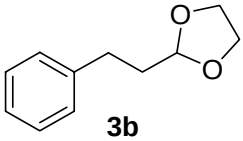
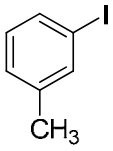
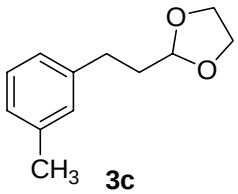
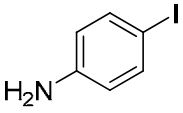
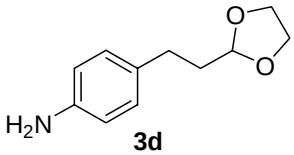
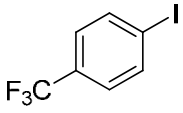
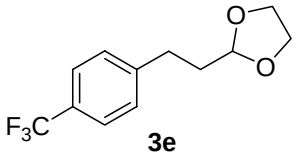
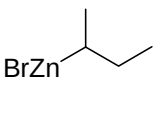
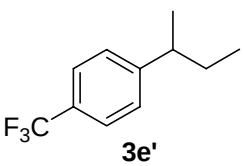
[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

Thus, the reaction in the optimized conditions takes place within few hours at room temperature. When using 10-fold lower catalyst loading (0.3%) the coupling product was obtained in 8 h with the same yield (80%) (**Table 1**, entry 11). Further reduction of the catalyst amount to 0.03% gave only 48% conversion in 24 h.

By means of this cross-coupling reaction we obtained Estragole derivative (**3a**), which has skin whitening effects.[143]

Results from **Table 2** represent that the reaction is general and tolerates the presence of different functional groups.

Table 2. *Ni-Catalyzed cross-coupling of aryl iodides with alkylzinc bromides*

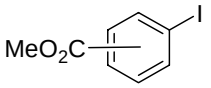
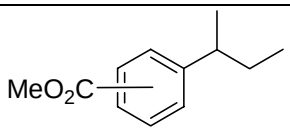
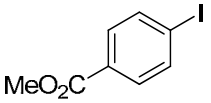
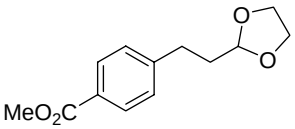
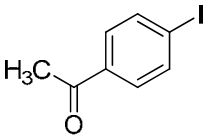
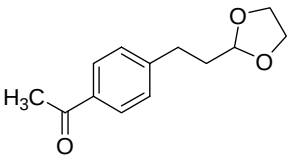
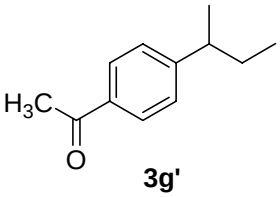
Entry	ArI	RZnBr	Product	t (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	3.5	80
2	 **1b**		 **3b**	9	78
3	 **1c**	**2a**	 **3c**	6	60
4	 **1d**		 **3d**	42	46
5	 **1e**		 **3e**	8	69
6		 **2b**	 **3e'**	3	58

[143] Motoki, Y.; Fujita, S.; Fujihara, Y.; Okada, Y.; Nombra, M. *J. Oleo Sci.* **2003**, *9*, 495-498.

Iodobenzene (**1b**) also coupled with **2a** in good yield (**Table 2**, entry 2). 4-Iodotoluene bearing an electron-donating group (methyl) (entry 3) gave the desired coupling product in moderate yield. Highly electron donating group such as amine, specifically 4-iodo aniline also cross-coupled in considerable yield (entry 4). There are some examples reported of palladium catalyzed Negishi reactions on haloanilines.[144] Flourinated compound **1e** containing an electron withdrawing group (entries 5 and 6) also afforded the coupling derivative although in moderate yields.

Besides, a wide variety of functional groups with electron-withdrawing character led to the cross-coupling products (**Table 3**).

Table 3. *Ni-Catalyzed cross-coupling of aryl iodides containing electron-withdrawing groups with alkylzinc bromides*

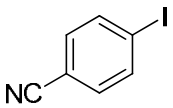
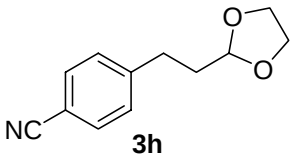
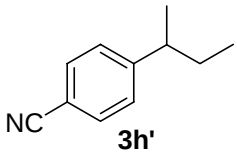
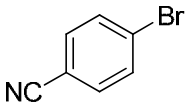
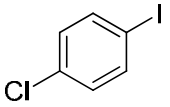
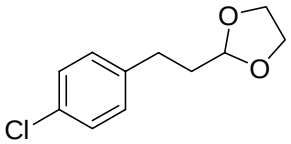
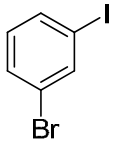
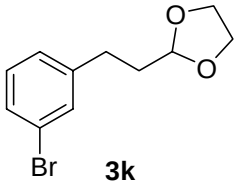
Entry	ArI	RZnBr	Product	t (h)	Yield (%)
1	 **1f-*o*** (*ortho*)	**2b**	 **3f-*o*** (*ortho*)	2	43
2	**1f-*m*** (*meta*)		**3f-*m*** (*meta*)	2	56
3	**1f-*p*** (*para*)		**3f-*p*** (*para*)	2	60
4	 **1f-*p***	**2a**	 **3f'**	12	75
5	 **1g**	**2a**	 **3g**	3	66
6		**2b**	 **3g'**	3	84

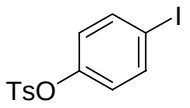
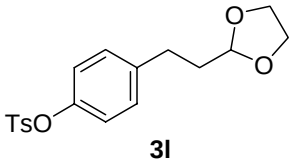
[144] (a) Russel, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943-949. (b) Jackson, R. F. W.; Moore, R. J.; Dexter, C. S. J. *J. Org. Chem.* **1998**, *63*, 7875-7884. (c) Rosowsky, A.; Chen, H. *J. Org. Chem.* **2001**, *66*, 7522-7526.

Modest results were obtained for esters (**Table 3**, entries 1, 2, and 3). Clearly the ester group present in the adjacent position to the reaction site, affected the cross-coupling process (**Table 3**, entry 1, **1f-*o***) leading to the final product in a lower yield. Thus, in addition to cross-coupling product with *ortho*-, *meta*-, and *para*-iodo methyl benzoate, a reduced product, i.e. methyl benzoate, was obtained in 16%, 15% and 7% yield respectively. However, *p*-iodo methyl benzoate reacted with **2a** providing the cross-coupling product in high yield, without formation of methyl benzoate as a side product (entry 4). Ketone derivatives (**Table 3**, entries 5, and 6) underwent the reaction with good yields.

Starting compounds containing Cl, Br or tosylate on the aromatic ring reacted chemoselectively through the C–I bond (**Table 4**, entries 4, 5, and 6, respectively).

Table 4. *Chemoselective Ni-catalyzed cross-coupling of aryl iodides and* p-*bromobenzonitrile with alkylzinc bromides*

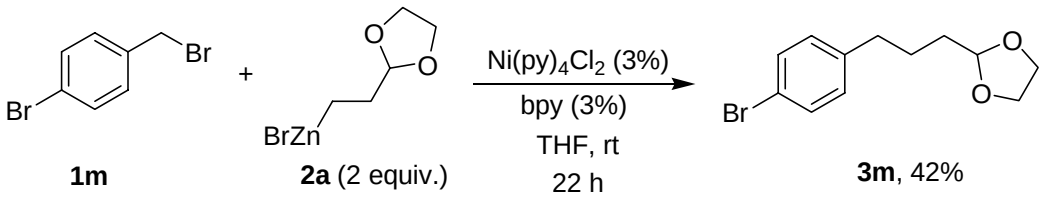
Entry	ArI	RZnBr	Product	t (h)	Yield (%)
1	 **1h**	**2a**	 **3h**	3	83
2	**1h**	**2b**	 **3h'**	3	65
3	 **1i**	**2b**	**3h'**	3	65
4	 **1j**	**2a**	 **3j**	2.5	75
5	 **1k**		 **3k**	2	75

6	 **1l**	 **3l**	9	65

p-Iodobenzonitrile also cross-coupled effectively under mild conditions. Aryl bromides showed lower reactivity under these conditions. Nevertheless, *p*-bromobenzonitrile (**1i**), which contain electron-withdrawing group, yielded the coupling product.

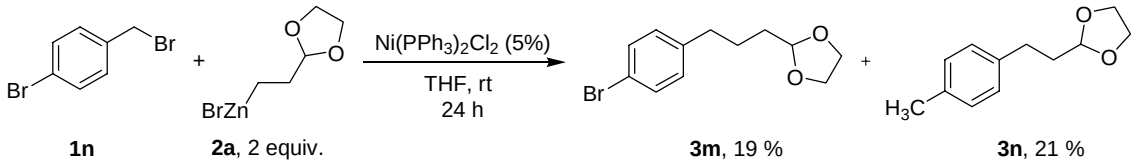
Instead, chlorobenzene, bromobenzene and *p*-bromoanisole were unreactive under the standard reaction conditions.

Benzylic bromides cross-coupled very slowly under standard reaction conditions and afforded the products with low yield. With the aim of checking the selectivity of this reaction versus halides containing at different hybridized electrophilic carbons, both substrates containing an aryl and an alkyl bromide was treated. *p*-Bromobenzyl bromide gave the corresponding cross-coupling product at benzylic position. Around 33% of the starting *p*-bromobenzyl bromide was recovered (**Scheme 1**).



Scheme 1

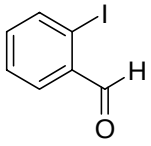
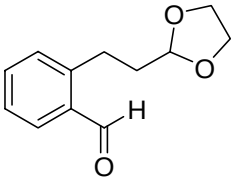
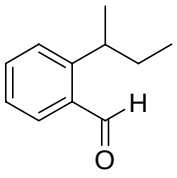
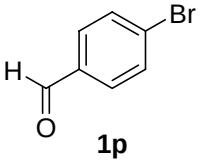
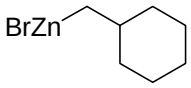
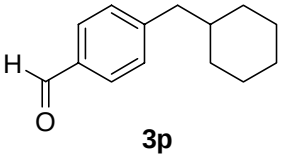
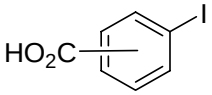
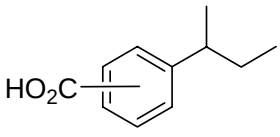
When *p*-bromobenzyl bromide was subjected to reaction under Ni-catalyst bearing phosphine ligands, a mixture of cross-coupling products was obtained, one product corresponded to alkylation of the benzylic position and the other at the arylic position with reduction of benzylic bromide. The reaction was incomplete and ~28% of starting material was recovered (**Scheme 2**).

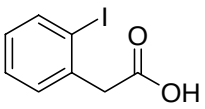
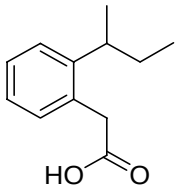


Scheme 2

o-Iodobenzaldehyde and *p*-bromobenzaldehyde reacted with alkylzinc reagents **2a** and **2b** with moderate to good yields (**Table 5**, entries 1, 2, and 3). Substrates containing other electron-withdrawing groups such as carboxylic acid (**Table 5**, entries 4, 5, and 6) also gave moderate to good yields. In addition to cross-coupling, benzoic acid is also obtained in 9%, 43% and 38% yield in the reaction of *o*-, *m*-, and *p*-iodobenzoic acids, respectively. Interestingly, the presence of free carboxylic acid group did not preclude the reaction (**Table 5**, entry 7). Thus, -CHO and -COOH functionalized iodobenzenes cross-coupled effectively, tolerating those sensitive functional groups under our simple Ni-catalysis conditions.

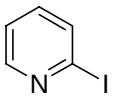
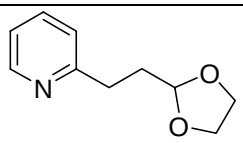
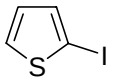
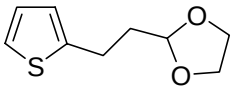
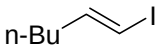
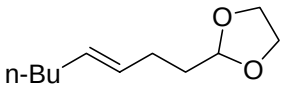
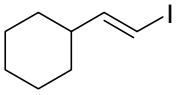
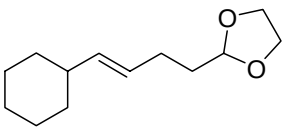
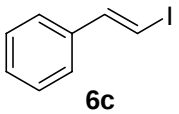
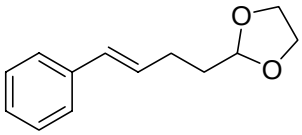
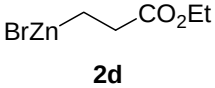
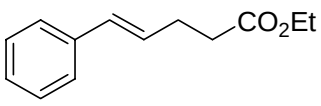
Table 5. *Ni-Catalyzed cross-coupling of aryl iodides containing aldehyde or carboxylic acid with alkylzinc bromides*

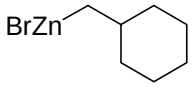
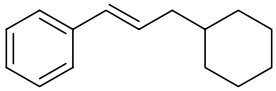
Entry	ArI	RZnBr	product	t (h)	Yield (%)
1	 **1o**	**2a**	 **3o**	8	52
2	**1o**	**2b**	 **3o'**	3	70
3	 **1p**	 **2c**	 **3p**	4	83
4	 **1q-*o*** (*ortho)*	**2b**	 **3q-*o*** (*ortho*)	1.5	89
5	**1q-*m*** (*meta*)		**3q-*m*** (*meta*)	1.5	50
6	**1q-*p*** (*para*)		**3q-*p*** (*para*)	1.5	56

7	 **1r**	**2b**	 **3r**	2	77

But the scope of this coupling is not limited to aryl derivatives. Heteroaromatic iodides such as 2-iodopyridine, and 2-iodothiophene successfully coupled, although longer reaction times were required (**Table 6**, entries 1, and 2). Alkenyl iodides (**Table 6**, entries 3-7) are also effective and afforded the desired cross-coupling derivatives in good yields.

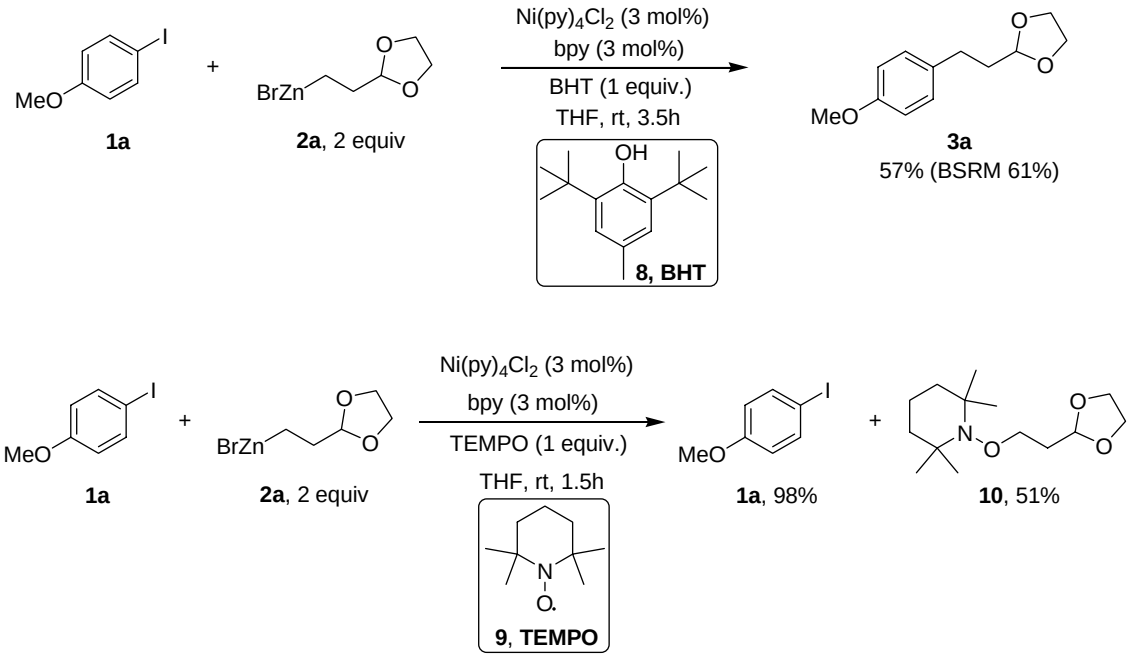
Table 6. *Ni-Catalyzed cross-coupling of heteroaryl and alkenyl iodides with alkylzinc bromides*

Entry	R-I	RZnBr	Product	t (h)	Yield (%)
1	 **4a**	**2a**	 **5a**	14	64
2	 **4b**	**2a**	 **5b**	12	65
3	 **6a**	**2a**	 **7a**	7	61
4	 **6b**	**2a**	 **7b**	1	71
5	 **6c**	**2a**	 **7c**	2	71
6	**6c**	 **2d**	 **7d**	11	51

7	**6c**	 **2c**	 **7e**	1	87

Instead, *p*-nitroiodobenzene was not effective, suggesting that radicals are involved in the reaction mechanism.

The reaction was performed in the presence of radical inhibitors in order to get insight into the reaction pathway, since it seemed that radicals could be involved. Nevertheless, when the reaction was performed in the presence of 1equiv of BHT, the yield of the coupling compound was only a bit lower (61%), suggesting that carbon radicals are not formed. Instead, the reaction was inhibited by the addition of TEMPO, which coupled with the alkyl fragment probably by reaction of the organozinc with an alkyl-Ni^{I} intermediate (*See chapter III for details*) (**Scheme 3**).[131]



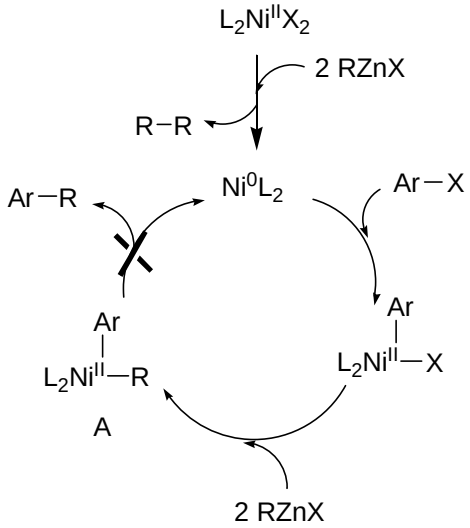
Scheme 3

Mechanistic aspects

We decided to explore computationally several possible mechanisms for the coupling between aryl halides and alkylzinc reagents. Two main pathways have been studied at DFT level (**Schemes 5**, and **8**). The first one relies on the formation of

[131] Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.

(alkyl)(aryl)-Ni^{II} complex **A**. This complex is formed by oxidative addition of the aryl halide to Ni(0) with subsequent transmetalation with the alkylzinc halide. Formation of organonickel(II) complexes as the first step of catalyzed reactions of aryl electrophiles is well established, and transmetalation on Ni(II) is also precedented in other metal-catalyzed reactions.[145] A reasonable pathway for the formation of the coupling product would involve C–C reductive elimination from complex **A** (**Scheme 4**).



Scheme 4.

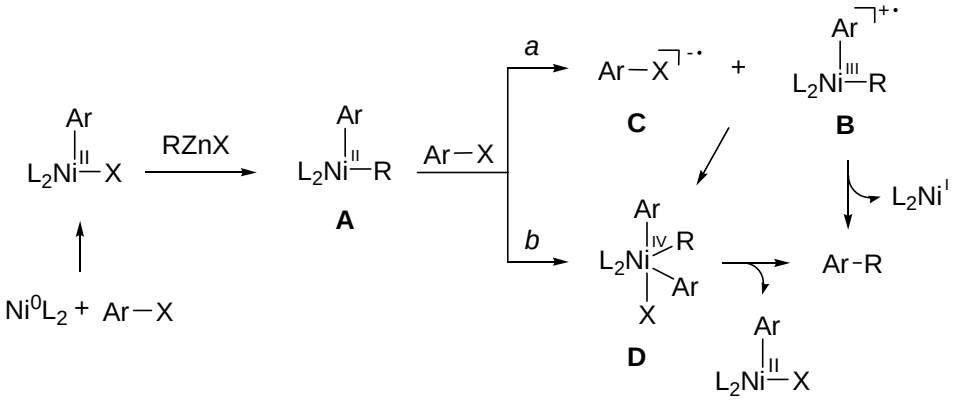
Nevertheless, studies on cross-coupling and homocoupling reactions have shown that the diorgano-Ni^{II} complexes formed after transmetalation, such as **A,** are unable to evolve by reductive elimination. Instead, complexes of type **A** must be previously oxidized by the haloarene to Ni^{III} derivative **B** and radical anion **C** by single electron transfer, prior to the C–C reductive elimination (pathway *a*, **Scheme 5**).[146,147] Ni^{III} derivative (**B**) produces cross-coupling product upon reductive elimination and evolves towards a Ni^{I} complex, which is the actual catalytically active species. Alternatively, oxidative addition of the aryl halide could furnish a Ni^{IV} intermediate (**D,** pathway *b*),

[145] Kochi, J. *Pure Appl. Chem.* **1980**, *52*, 571-605.

[146] Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *72*, 7262-7270.

[147] Recently, it has been shown that complexes of bidentate bis(trialkyl)phosphines with CF_3 and aryl ligands do not afford trifluorotoluenes, even in the presence of oxidants: Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vicic, D. A. O*rganometallics* **2008**, *27*, 3933-3938.

which could be also formed by collapse of the ion pair in pathway *a*. A final reductive elimination from either **B** or **D** would afford the coupling compound.



Scheme 5

For this alternative we studied the reaction of a model of complex **A** shown in **Scheme 5** (L_2 = bpy, R = CH_3, Ar = Ph). Formation of **A** constitutes a feasible and well documented process.[146,147] High activation energies (*ca.* 30 kcal mol^{-1}) were obtained for both the oxidative addition of PhI to **A** to give complexes **D** with different geometries (pathway *b*), and for the formation of **D** by reaction between **C** and **B**.[148] Moreover, reductive elimination from **B** associated to **C** as a radical ion pair is also prohibited (E_a = 27 kcal mol^{-1}). Therefore, the mechanisms outlined in **Scheme 5** could be disregarded. For computational details see *Computational section, III. Computational study of the oxidative addition of PhI to (bpy)Ni(Me)Ph*).

As we have mentioned above, the failure to couple nitroaromatic halides indicated that the reaction may involve radical complexes in the reaction pathway. The intermediacy of radicals in Ni-catalyzed reactions has been well established in some

[146] Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *72*, 7262-7270.

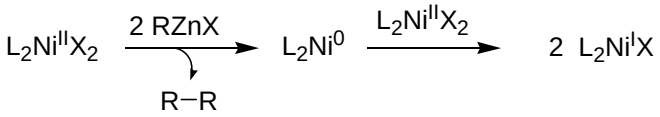
[147] Recently, it has been shown that complexes of bidentate bis(trialkyl)phosphines with CF_3 and aryl ligands do not afford trifluorotoluenes, even in the presence of oxidants: Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vicic, D. A. O*rganometallics* **2008**, *27*, 3933-3938.

[110] Stille coupling: Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510-511.

[148] Although DFT calculations with the basis set used cannot be employed for calculation of reliable absolute energies, the calculated activation energy values are much higher than those we obtained with the same approximations in our previous studies. For that reason and for the low activation energies we have found for the alternative pathways, we may disregard these mechanisms.

cases, such as the Ni-promoted aryl–aryl coupling of aryl halides in the presence of phosphines,[145] or bpy.[149]

Other metal-catalyzed coupling reactions seem to follow radical mechanisms as well.[39,107,110,111] The classical mechanism of the aryl–aryl coupling of aryl halides starts with oxidative addition of the haloarene a Ni^0 complex to give an aryl-Ni^{II} derivative in the initiation process. Propagation steps of the radical chain reaction involve activation of the haloarene by Ni^I species to give Ni^{III} derivatives. On the other hand, alkyl–alkyl Negishi cross-couplings have been developed in recent years (*see section IIe from Introduction*), and mechanistic evidence has been obtained both experimentally and computationally.[130] These reactions have been proposed to involve radical Ni^I derivatives as the actual catalysts, which activate the alkyl halides by oxidative addition.[127,129,133b,150] In this case, a Ni^I-Ni^{III} catalytic cycle takes place. Ni^I complexes may be formed from Ni^{II} precursors with alkylzinc halides in the presence of nitrogen terdentate ligands by comproportionation of Ni^{II} intermediates with Ni^0 species formed by reductive elimination of dialkyl-Ni^{II} complexes, and forms homocoupling product as a side product (**Scheme 6**).[129,151]



Scheme 6

[145] Kochi, J. *Pure Appl. Chem.* 1980, **52**, 571-605.

[149] Klein, A.; Budnikova, Y. H.; Sinyashin, O. G. *J. Organomet. Chem.* **2007**, *692*, 3156-3166.

[39] Powell, D. A.; Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788-7789.

[107] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341.

[110] Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510-511.

[111] Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3962-3965.

[130] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680-3688.

[127] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100-8101.

[129] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

[133b] Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211-4213.

[150] Anderson, T. J.; Vicic, D. A. *Organometallics* **2004**, *23*, 623-625.

[151] In fact, homocoupling products of the alkylzinc bromides are observed in all reactions in *ca.* 6% yield, which supports formation of Ni^0 intermediates.

Alkyl-Ni^{I} complexes containing terdentate ligands such as terpyridine or pybox derivatives show the unpaired electron delocalized on the π-orbitals of the ligand, and exhibit square planar geometry. For these reasons they may be described as Ni^{II} complexes with two formally anionic ligands. We have computed the singly occupied molecular orbital (SOMO) for the methyl-Ni derivative containing a Me-pybox ligand (**Figure 1**).[131]

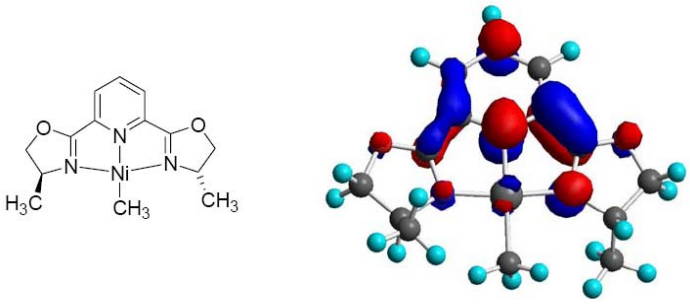
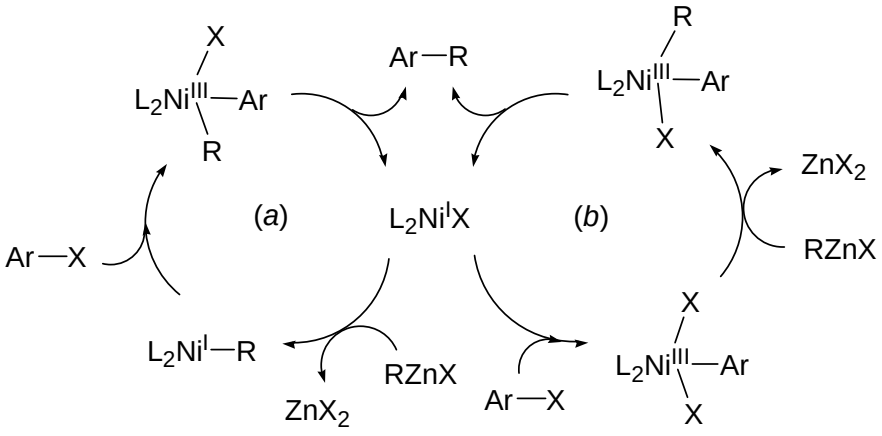


Figure 1. *Complex* **(Me-pybox)NiMe** *showing the ligand-centered single occupied molecular orbital.*

The unpaired electron prefers to delocalize on the conjugated system, and since it does not occupy the $d_{x^2-y^2}$ orbital, the complex remains in the typical square-planar geometry for Ni(II) derivatives, albeit it may be considered formally a Ni(I) derivative.

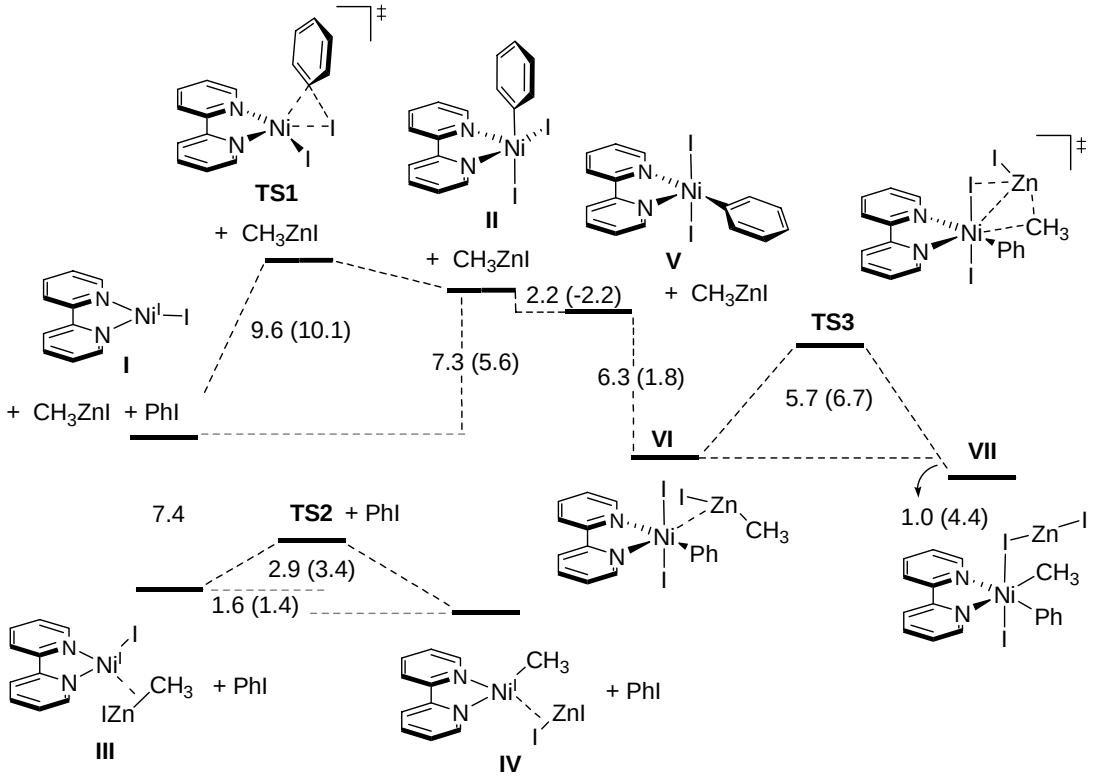
In accord with these precedents, we considered other mechanistic alternatives, involving Ni^{I}-Ni^{III} catalytic cycles (**Scheme 7**). In the first cycle (*a*) transmetalation takes place on Ni^{I} before oxidative addition of the aryl halide. In the second cycle (*b*), the active catalyst oxidatively adds the haloarene, and the resulting Ni^{III} complex reacts with the alkylzinc halide.



Scheme 7

[131] Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.

Calculations were performed with Gaussian 03 at DFT level (see *Computational section*, p 230). We chose Ni(bpy)I (**I**, **Scheme 8**) as the model for the computational study. Although alkylzinc bromides have been employed in the experiments, we have used iodine as the only halogen for our calculations in order to simplify the number of possible isomeric species that could be involved. The profiles for the reaction of **I** with PhI and MeZnI through oxidative addition and transmetalation, respectively, are shown in **Scheme 8**.

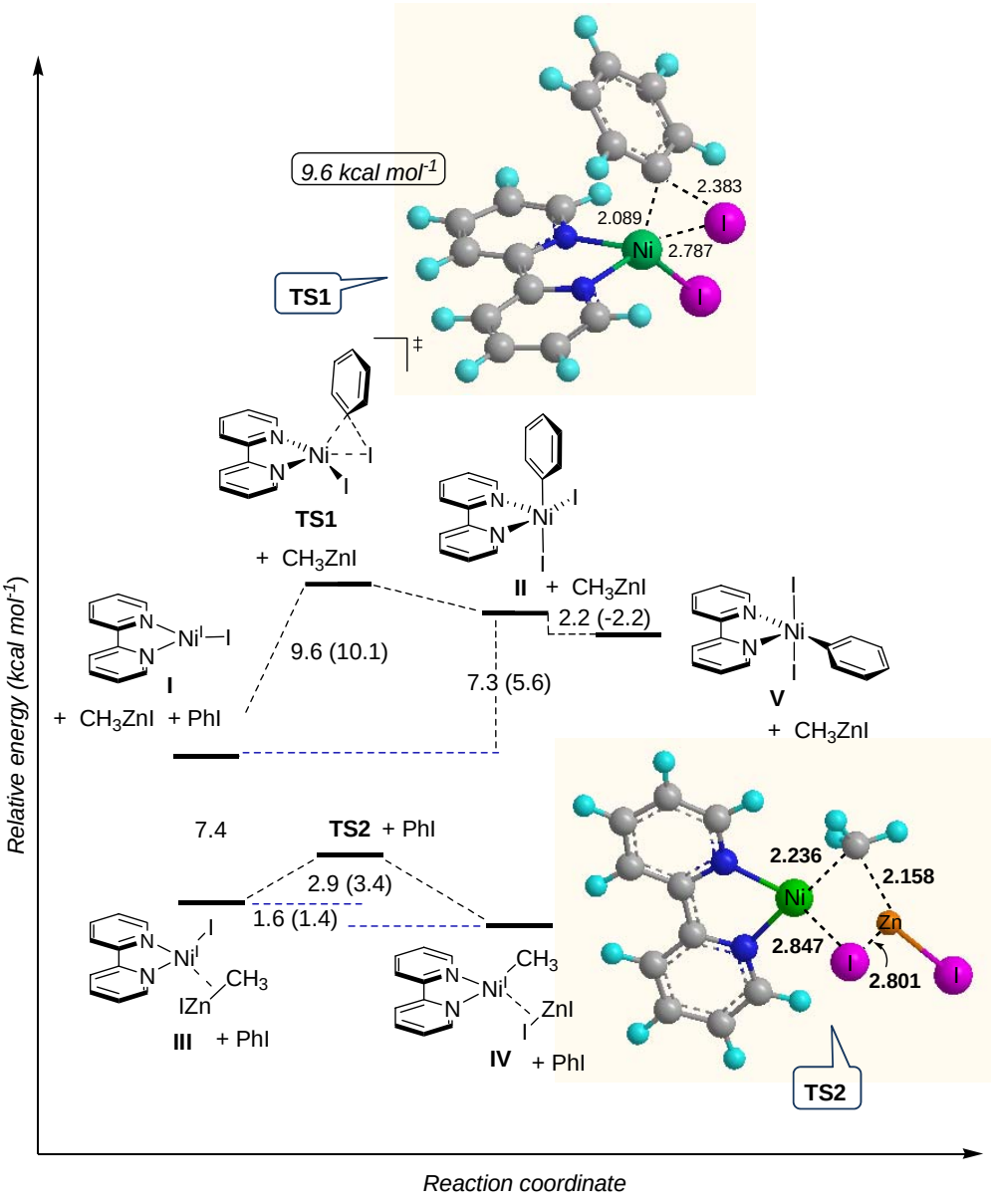


B3LYP/6-31G(d) (C, H, N), LANL2DZ (Ni, Zn, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets.

Scheme 8

Oxidative addition of PhI to **I** to give pentacoordinated **II** is endothermal and takes place through **TS1** (**Scheme 9**) with an activation energy of 9.6 kcal mol^{-1}. The reverse C–I reductive elimination from **II** shows very low activation energy (2.3 kcal mol^{-1}) and is thermodynamically favoured. Moreover, coordination of THF to **I** is exothermic (-6.6 kcal mol^{-1}), and the actual activation energy for the formation of **TS1** from the entry channel may be even higher. Nevertheless, the energy values shown correspond to the electronic energy corrected with the zero-point vibrational energy, and

they reflect the intrinsic reactivity of the different species.[152] In contrast, association of MeZnI to **I** affords complex **III** exothermically (-7.4 kcal mol^{-1}), and subsequent intramolecular transmetalation through **TS2** is a fast process (E_a = 2.9 kcal mol^{-1}) **(Scheme 9)**.

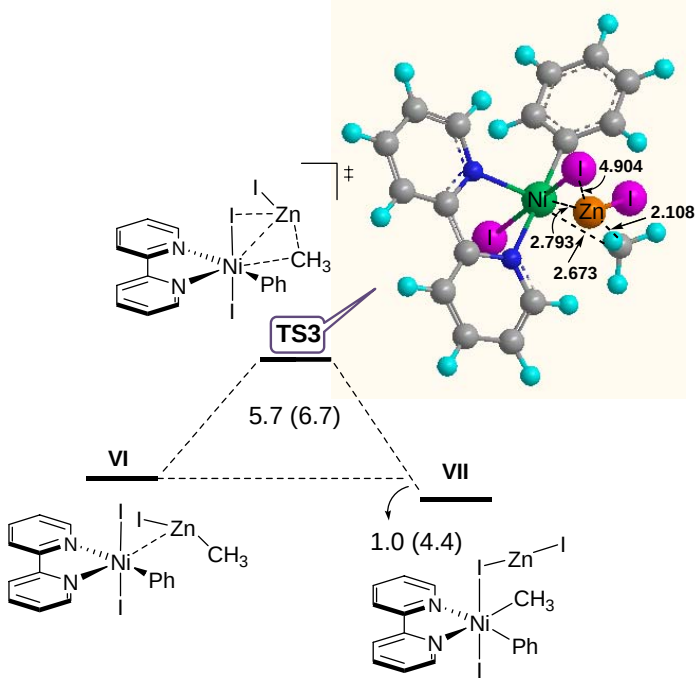


Energy differences in THF calculated with the PCM model are shown in brackets; Figure includes the geometry of the **TS1** *and* **TS2**, *in which specified distances are in Å.*

Scheme 9

[152] Free energies can be found in the *Computational section*. These values are affected by errors derived from the calculation of entropy and do not reflect the solvation processes involved. It is important to note that the alkylzinc reagents and the resulting ZnI_2 will be coordinated to THF.

We have calculated the possible evolution of **II** to the coupling product. Exothermic coordination of MeZnI (-6.3 kcal mol^{-1}) to **V** (an isomer of **II**)[153] affords intermediate **VI**, which evolves to **VII** through **TS3** (E_a = 5.7 kcal mol^{-1}) almost thermoneutrally (-1.0 kcal mol^{-1}, **Scheme 10**). For the lower energy pathway, we were not able to locate a transition state for the oxidative addition of PhI to complex **IV**, and therefore, the calculated profiles for different pathways cannot be directly compared after this stage.



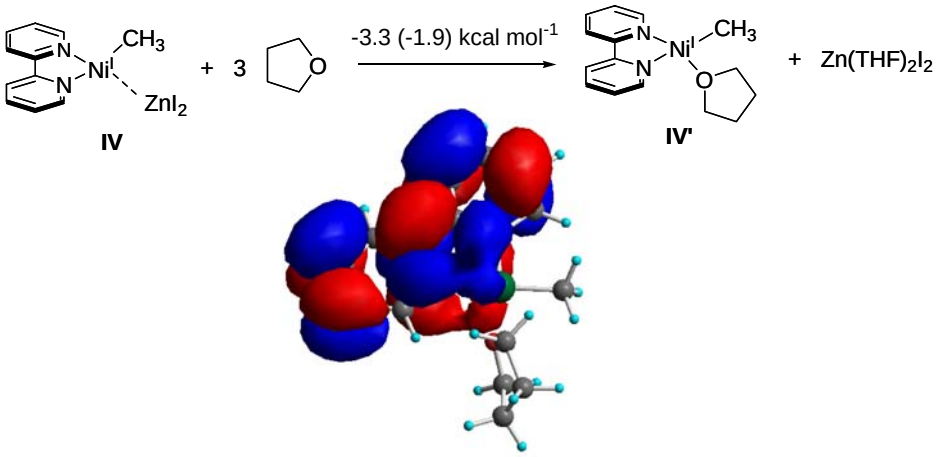
B3LYP/6-31G(d) (C, N, H), LANL2DZ (Ni, Zn, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets; Figure includes the geometry of the **TS3***, in which specified distances are in Å.*

Scheme 10

Complex **IV** is expected to release solvated ZnI_2 in solution. In fact, the energy for the reaction of **IV** with three molecules of THF to give **IV'** plus $Zn(THF)_2I_2$ is computed to be exothermic (-3.3 kcal mol^{-1}, **Scheme 11**). Interestingly, inspection of

[153] Pentacoordinated complexes **V** and **II** show similar stabilities (**V** is 2.2 kcal mol^{-1} more stable than **II** in the gas phase, and the **II** is calculated to be 2.2 kcal mol^{-1} more stable in THF), and facile isomerization could take place according to the behaviour of different starting structures during the geometry optimization calculations. We have not attempted to locate transition states for these isomerizations.

the SOMO of complex **IV'** shows the unpaired electron is delocalized on the ligand (bpy), as it has occurs for the terpy and pybox complexes previously described.[129,131]



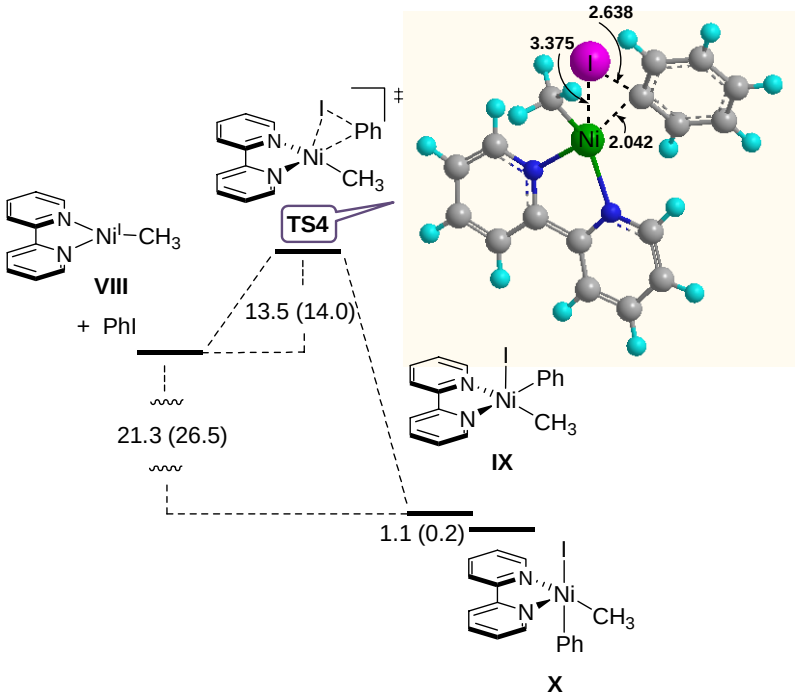
B3LYP/6-31G(d) (C, N, H), LANL2DZ (Ni, Zn, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets.

Scheme 11

THF decoordination from **IV'** to give **VIII** is thermoneutral, and for that reason we have considered convenient to use this intermediate to compute the evolution of the alkyl-Ni^{I} species. The calculated E_a for the oxidative addition of PhI to **VIII** is 13.5 kcal mol^{-1} (**Scheme 12**). Product **IX** is the same structure that would be formed by dissociation of ZnI_2 from **VII**. Thus oxidative addition of Ph-I to **I** would be rate-limiting step for the higher energy mechanisms Reductive elimination from complex **X** (isomer of **IX**), which is common for both pathways, is very fast and strongly exothermic and would regenerate the catalytically active species (**Scheme 12** and **Scheme 13**). According to the exothermic solvation of **IV**, we would expect that transition state **TS4** lied below the energy of (**TS1** + MeZnI).

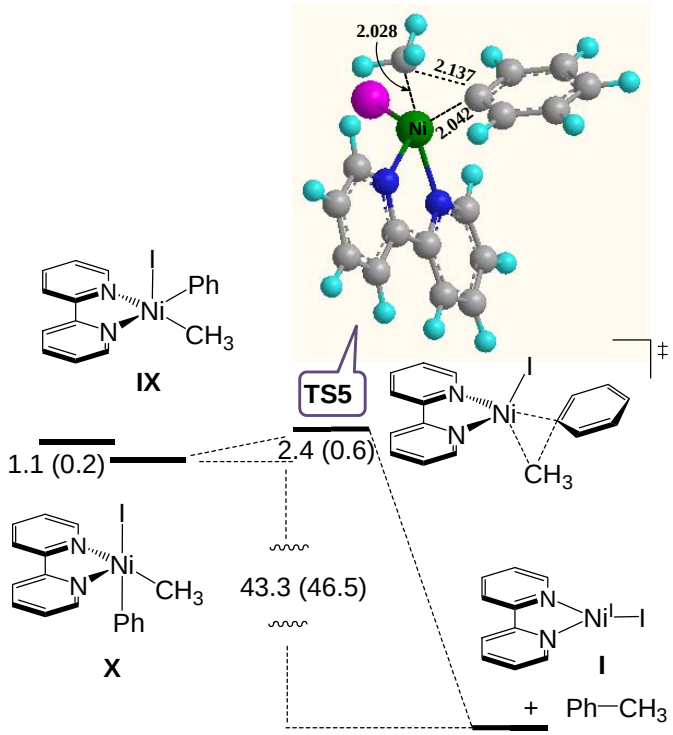
[129] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

[131] Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.



B3LYP/6-31G(d) (C, N, H), LANL2DZ (Ni, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets; Figure includes the geometry of the **TS4***, in which specified distances are in Å.*

Scheme 12



B3LYP/6-31G(d) (C, N, H), LANL2DZ (Ni, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets; Figure includes the geometry of the **TS5***, in which specified distances are in Å.*

Scheme 13

Therefore, our results suggest that the actual catalytic cycle involves an initial transmetalation of the Ni^{I} intermediate with the alkylzinc halide to give an alkyl-Ni^{I} complex, which then reacts with the aryl halide affording a diorgano-Ni^{III} intermediate, as depicted in **Scheme 7 (a)**. The observed reaction product when TEMPO is added suggests the formation of alkyl-Ni^{I} species and further supports this mechanism. Calculations of the reaction and activation energies in THF with PCM model (shown in schemes into brackets) led essentially to the same results. The main difference is the relative stability of intermediates **II** and **V** (**Scheme 8**). Complex **V** is 2.2 kcal mol^{-1} less stable than **II** in this case. Additionally, **TS3** is relatively destabilized and lies 2.6 kcal mol^{-1} above (**TS1** + MeZnI), thus becoming the highest energy stationary point for this pathway, which does not affect the conclusions stated above.

It is important to note that, although Ni^{I}-Ni^{III} catalytic cycles seem to operate in other Ni-catalyzed cross-coupling reactions, the role of the different oxidation states and the activation of the electrophile are not the same as in the case we present here (**Scheme 14**). As it has been mentioned above, Ni^{I} complexes activate haloarenes in the propagation step of aryl–aryl couplings. The proposed active species does not contain a carbon ligand.[145] In contrast, in alkyl–alkyl couplings, activation of the electrophile is performed by an alkyl-Ni^{I} complex, which is formed by transmetalation with the alkylzinc halide.[127,129] Very recently, the first computational study of the complete catalytic cycle for the Pd-mediated alkyl–alkyl Negishi reaction is also reported, and disclosed that the bulky NHC ligands introduce important differences into the traditionally accepted mechanism.[69]

In a recent computational study of this reaction involving terdentate ligands, transmetalation was calculated to be endoergic and no transition state for this process could be found.[130] Subsequent oxidative addition of the haloalkane takes place in two steps. The alkyl-Ni^{I} complex homolytically cleaves the C–X bond, affording an alkyl-Ni(II)-X species and a carbon radical, which coordinates to the metal complex to afford

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[145] Kochi, J. *Pure Appl. Chem.* 1980, **52**, 571-605.

[127] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100-8101.

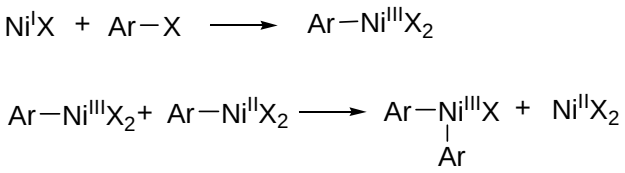
[129] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

[69] Chass, G. A.; O'Brien, C. J.; Hadei, N.; Kantchev, E. A. B.; Mu, W. -H.; Fang, D. -C.; Hopkinson, A. C.; Csizmadia, I. G.; Organ, M. G. *Chem. Eur. J.* **2009**, *15*, 4281-4288.

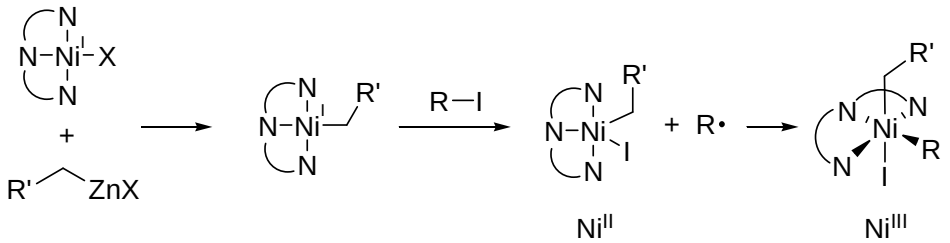
[130] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680-3688.

the key diorgano-Ni^{III} derivative from which reductive elimination takes place (**Scheme 14**, **b**). For aryl–alkyl coupling, we have found that transmetalation is an exothermic and fast process when bidentate *N*-ligands are used. This suggests that transmetalation in alkyl–alkyl couplings could take place through intermediates containing bidentate ligands.

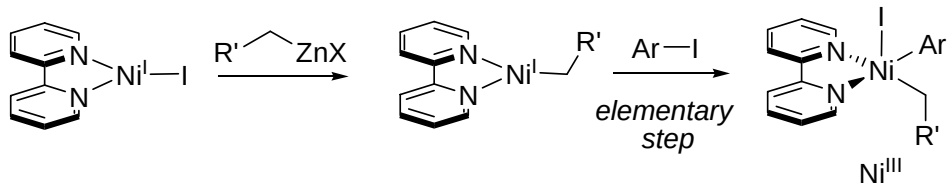
a) Homocoupling of haloarenes



b) Alkyl-alkyl Negishi cross-coupling



c) Alkyl-aryl Negishi cross-coupling



Scheme 14

II. Nickel-catalyzed cross-coupling reaction of C(sp^3) electrophiles with alkylzinc and alkylmagnesium halides

IIa. Nickel-catalyzed cross-coupling reaction of alkyl halides with alkylzinc bromides

As it has been stated in the previous sections, most studies on Pd and Ni-catalyzed cross-coupling reactions have focused on the formation of C(sp^2)–C(sp^2) (particularly biaryl) and C(sp^2)–C(sp^3) bonds.[1] Transition metal-catalyzed cross-coupling reactions between C(sp^3) centers are rare, especially those with *β*-hydrogen atoms represent a more difficult class of electrophiles for cross-coupling reactions than the corresponding vinyl or aryl halides.

Alkyl electrophiles containing *β*-hydrogen atoms were originally seen as unsuitable substrates for transition-metal catalyzed cross-coupling reactions. The oxidative addition of aliphatic C−X bonds to a metal center is considerably more difficult than the oxidative addition of aryl and alkenyl C−X bonds, as C(sp^3)−X bonds are more electron-rich than C(sp^2)−X bonds. The alkyl metal species that results is also substantially less stable than an aryl or alkenyl metal species owing to a lack of π electrons available to interact with the empty *d*-orbitals of the metal center. This instability renders the alkyl metal intermediate prone to side reactions, such as *β*-hydride elimination or hydrodehalogenation, which can outcompete both intermolecular transmetalation and reductive elimination (**Scheme IV** from *Introduction*, p 52).

To date there is a very limited number of precedents reported regarding the possibility of forming C–C bonds between C(sp^3) centers. Although copper-catalyzed cross-coupling of alkylmagnesium reagents was known, its utility is limited due to the low chemoselectivity as a result of the high reactivity of the Grignard reagents.[154]

Early investigations by Tucker and Knochel focused on the reactions of alkyl iodides with dialkyl zinc reagents in the presence of stoichiometric quantities of

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[1] (a) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, 1998. (b) *Metal-catalysed Cross-coupling Reactions*, de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, 2004.

[154] (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572-4580. (b) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451-4454.

$[Cu(CN)Me_2\text{-}MgCl_2)]$.[155] However, the use of stoichiometric amounts of copper salts precludes large scale applications. So, there was the need for a transition metal-*catalyzed* cross-coupling reaction between two $C(sp^3)$ centers. Shortly afterwards, Knochel and co-workers reported a nickel-catalyzed cross-coupling between $C(sp^3)$ centers. The introduction of a double bond at the 4- or 5- position of the alkyl iodide made possible this first efficient purely nickel-catalyzed alkyl–alkyl cross-coupling reaction. The reductive elimination of the coupling product is facilitated by intramolecular coordination of the double bond and can be further enhanced by electron-withdrawing substituents on the double bond.[120] The reaction proceeds in the presence of $[Ni(acac)_2]$ (7 mol%) in a THF/NMP solvent mixture. However, the generality of this method is clearly limited by the structural requirements (see *Introduction*, p 94).

A few years later, Knochel and co-workers extended the scope of this methodology with a similar protocol that exploited intermolecular olefin coordination at the nickel catalyst. In this case the $[Ni(acac)_2]$-catalyzed coupling of alkyl iodides, which now no longer require a pendant double bond for coordination to the metal center, could be effected by adding a π-acceptor ligand, such as acetophenone, benzophenone, or a styrene derivative. A screening of different ligands identified 3-trifluoromethylstyrene as the most effective cocatalyst (see *Introduction*, p 93).[121] The optimized reaction conditions tolerate a wide range of functional groups. In subsequent studies the reaction was extended to the more stable and convenient alkylzinc halides.[123] More recently, Fu has reported 4% $Ni(cod)_2$/8% *s*-Bu-pybox-catalyzed alkyl–alkyl couplings of alkylzinc halides with secondary iodides and bromides in DMA (see *Introduction*, p 95).[124] The use of optically active pybox-based ligands has allowed developing the first method that achieves catalytic asymmetric cross-coupling of alkyl

[155] Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781-4782.

[120] Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544-3553.

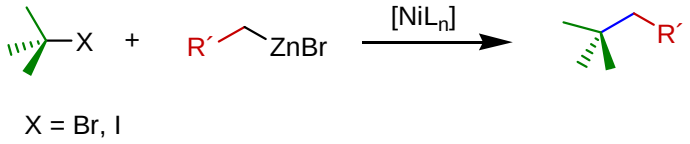
[121] Giovannini, R.; Stüdemnann, N.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390.

[123] Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79-85.

[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

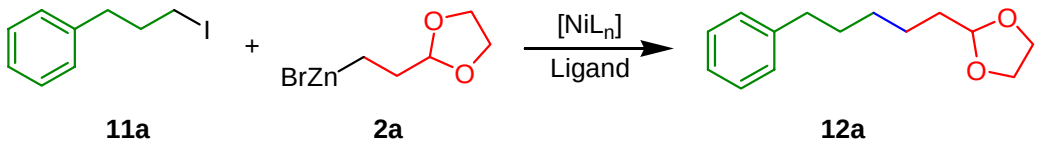
electrophiles.[126] Alkyl–alkyl Negishi cross-couplings can be also catalyzed by Pd complexes when using heterocyclic carbene ligands.[68]

This section includes the development and study of selected examples of nickel-catalyzed cross-coupling of alkyl bromides or iodides with alkylzinc bromides for $C(sp^3)$–$C(sp^3)$ bond formation (**Scheme 15**).



Scheme 15

We first studied the reaction of primary alkyl iodide **11a** (which can be easily prepared by reaction of commercially available 1-chloro-3-phenylpropane and NaI) with alkylzinc bromides (**Scheme 16**).



11a **2a** **12a**

Scheme 16

We initially evaluated the conditions reported by Fu, and changed the ligand and the starting Ni-complex. By replacing air and moisture unstable $Ni(cod)_2$ by more convenient, air and moisture stable blue complex $[Ni(py)_4Cl_2]$[141] along with terpyridine a good yield was observed (63% in 24 h). We tried other nitrogen-based terdentate ligand based on the pybox skeleton, and the di-*sec*-butyl derivative gave the best results, according to what had been previously observed by Fu in simple cross-couplings.[124] So, $Ni(py)_4Cl_2$ along with (*S*)-(*sec*-Bu)-pybox, proved to be an effective catalyst for the

[126] Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483.

[68] Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805-3807.

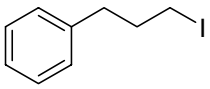
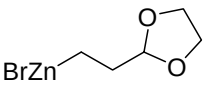
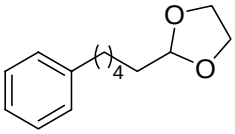
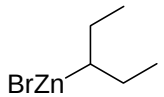
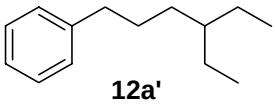
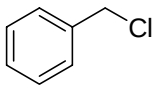
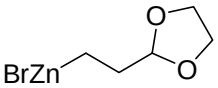
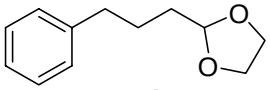
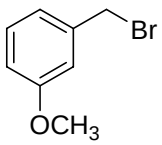
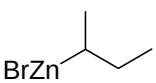
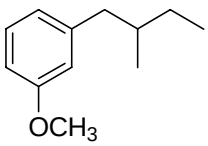
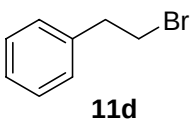
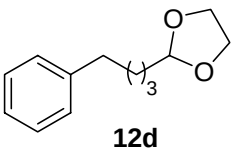
[141] (a) Long, G. J.; Clarke, P. J. *Inorg. Chem.* **1978**, *17*, 1394-1401. (b) Bachman, R. E.; Whitmire, K. H.; Mandal, S.; Bharadwaj, P. K. *Acta Crystallogr. Sect. C* **1992**, *C48*, 1836-1837.

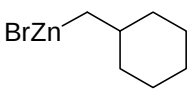
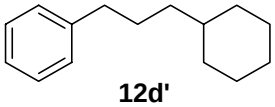
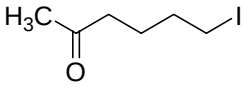
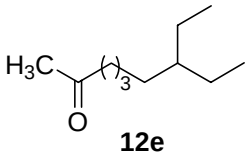
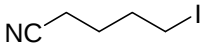
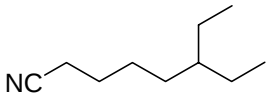
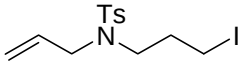
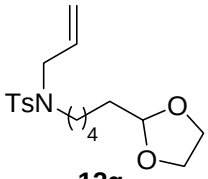
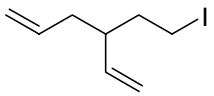
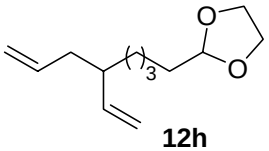
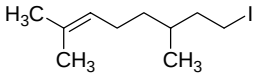
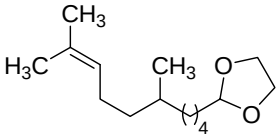
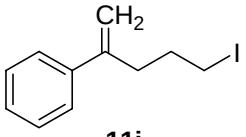
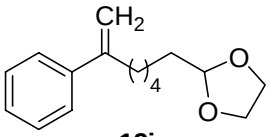
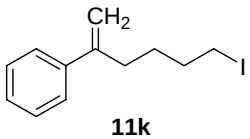
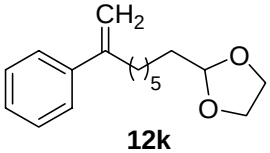
[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

simple alkyl–alkyl coupling of **11a** with alkylzinc bromide (**2a**) and gave even higher yield, 69% in 11 h, (**Table 7**, entry 1). Homocoupling compound derived from the alkylzinc bromide was isolated in *ca*. 10% yield (in relation to the starting nucleophile) in most cases. The use of smaller amounts of the nucleophile led to lower yields.

A variety of alkyl bromides and iodides afforded the desired coupling derivatives with alkylzinc bromides by using this catalytic system. Primary alkyl iodide **11a**, also cross coupled with secondary alkyl zinc reagent (**2e**) in moderate yields (**Table 7**, entry 2). Remarkably, benzyl chloride and substituted benzyl bromide coupled with alkylzinc reagents **2a** and **2b**, respectively, in high yield (**Table 7**, entries 3, and 4). (2-Bromoethyl)benzene also coupled efficiently with alkylzinc bromide (**Table 7**, entries 5, and 6). So, these results allowed us to speculate that the chelating pybox ligand disfavors *β*-hydride elimination, which requires a vacant coordination site on the metal center.

Table 7. *Ni-Catalyzed cross-coupling of primary alkyl halides with alkylzinc bromides*[a]

Entry	Substrate	RZnBr	Product	t (h)	Yield (%)
1	 **11a**	 **2a**	 **12a**	11	69
2	**11a**	 **2e**	 **12a'**	18	61
3	 **11b**	 **2a**	 **12b**	2	71
4	 **11c**	 **2b**	 **12c**	1	63
5	 **11d**	**2a**	 **12d**	11	73

6	**11d**	 **2c**	 **12d'**	8	62
7	 **11e**	**2e**	 **12e**	11	66
8	 **11f**	**2e**	 **12f**	11	71
9	 **11g**	**2a**	 **12g**	18	63
10	 **11h**	**2a**	 **12h**	5	66
11	 **11i**	**2a**	 **12i**	8	76
12	 **11j**	**2a**	 **12j**	9	82
13	 **11k**	**2a**	 **12k**	11	69

[a]Conditions: $[Ni(py)_4Cl_2]$ (10 mol %), (*S*)-(*sec*-Bu)-pybox (10 mol %), 4 equiv RZnBr in THF at 23 ºC.

Alkyl chlorides, and tertiary alkyl bromides did not react under these conditions. However, under our Ni-catalytic system, the transformation proceeded in the presence of various functional groups, such as ketone and cyano (**Table 7**, entries 7, and 8) in 66

and 71% yield, respectively. Tosylamides were also compatible with our reaction conditions. Thus the reaction of **11g** with **2a** led the cross-coupling product in 63% yield (**Table 7**, entry 9).

As discussed later (see section ***IV.*** *Ni-catalyzed cascade formation of C(sp^3)–C(sp^3) bonds by cyclization and cross-coupling reactions of iodoalkanes with alkylzinc bromides*, p 206), an alternative mechanism may operate in this reaction. Taking into account this possibility, the presence of the double bond not only may facilitates reductive elimination by intramolecular coordination, but might participate in the reaction by offering an opportunity for the cyclization and subsequent intermolecular coupling, which would lead to the formation of two C(sp^3)–C(sp^3) bonds. However, we obtained only a coupling product rather than cyclization/cross-coupling process. Entries 8-13 (**Table 7**) showed only efficient couplings, in spite of the presence of a double bond. The formation of cyclic derivatives from citronellyl iodide **11i** (**Table 7**, entry 11) was not observed either.

A variety of transition metals, such as palladium, nickel, iron, cobalt, and copper, mediate the ready coupling of a wide range of primary alkyl halides with organometallic reagents containing zinc, boron, silicon, tin, and magnesium to some extent.[156] In contrast, the cross-coupling of secondary alkyl halides remains a challenging task. The added steric hindrance of a secondary alkyl halide increases the energy barrier to oxidative addition and thus makes traditional transition metal-catalyzed processes much more difficult.[157] Nevertheless, there has been a dramatic rise in the development of cross-coupling reactions of secondary alkyl halides, particularly in the last five years. The development of these new methodologies is significantly expanding the scope of transition metal-catalyzed processes.

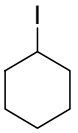
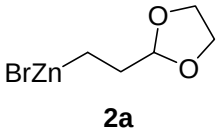
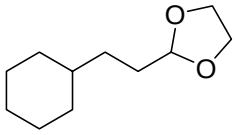
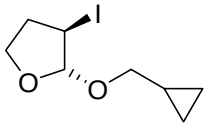
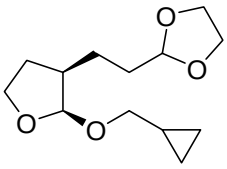
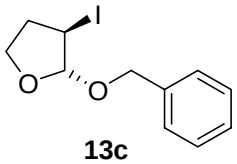
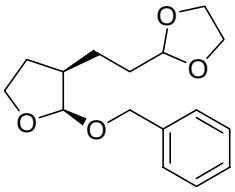
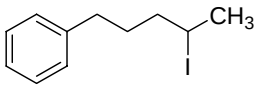
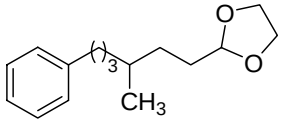
So, we intended to develop the cross-coupling of secondary alkyl halides, which is comparatively less explored. Under our optimized conditions secondary alkyl iodides also cross-couple effectively with primary alkylzinc bromides in high yield (**Table 8**, entrries 1-4).

---

[156] A review on metal-catalyzed couplings of alkyl halides: Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.

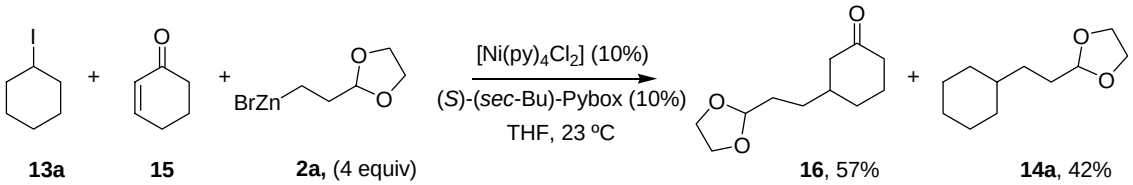
[157] For studies with palladium see: Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749-5752.

Table 8. *Ni-catalyzed cross-coupling of secondary alkyl halides*[a]

Entry	Substrate	RZnBr	Product	t (h)	Yield (%)
1[b]	 **13a**	 **2a**	 **14a**	11	74
2[c]	 **13b**	**2a**	 **14b**	6	79
3[c]	 **13c**	**2a**	 **14c**	16	72
4	 **13d**	**2a**	 **14d**	3	73

[a]Conditions: $[Ni(py)_4Cl_2]$ (10 mol %), (*S*)-(*sec*-Bu)-pybox (10 mol %), 4 equiv. RZnBr in THF at 23ºC. [b]If tpy is used as a ligand, isolated yield is 51%. [c]The relative stereochemistry shown is the most probable for the major isomer, but it is tentative. NOE data are consistent with this relative configuration, but overlapping of signals in the ^{1}H NMR spectra precludes confirmation.

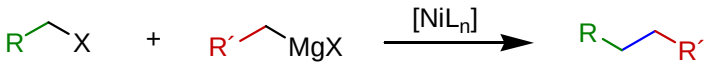
Finally, we also tested the intermolecular three-component coupling of an alkyl halide, an enone and alkylzinc bromide. In this case, we just observed a mixture of coupling products, one of them resulting from the 1,4-addition (57% yield) and the other one the direct coupling between the alkyl iodide and the alkylzinc bromide (42% yield) (**Scheme 17**).



Scheme 17

IIb. Nickel-catalyzed cross-coupling reaction of alkyl halides with alkylmagnesium halides

During the past decade, remarkable progress has been brought about in cross-coupling using alkyl halides by many groups using various transition metal catalysts.[25a, 140,27,109 ,158] Pd and Ni-catalyzed cross-couplings using alkyl Grignard and alkylzinc reagents could afford alkyl chains, which is an area of major interest as it is one of the least developed (**Scheme 18**).



Scheme 18

Kambe *et al.* enormously contributed to the cross-coupling of alkyl halides with alkylmagnesium halides in the presence of additives. Nickel and Cu-catalyzed versions permitting alkyl–alkyl coupling show wide applicability. Even alkyl fluorides cross-couple efficiently with alkyl and arylmagnesium reagents.[135] As an extension of this study, Kambe employed tetraene as an additive under Ni-catalysis to achieve alkyl–alkyl coupling (see page 101).[136]

This section includes the study of selected examples of nickel-catalyzed cross-coupling of primary alkyl iodides with alkylmagnesium reagents for $C(sp^3)$–$C(sp^3)$ bond formation.

For the optimization of reaction conditions to afford alkyl–alkyl cross-coupling reaction, we first studied the reaction of primary alkyl iodide **11a** with alkylmagnesium

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[25a] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3018-3020.

[140] Luh, T.; Leung, M; Wang, K. *Chem. Rev.* **2000**, *100*, 3187-3204.

[27] Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

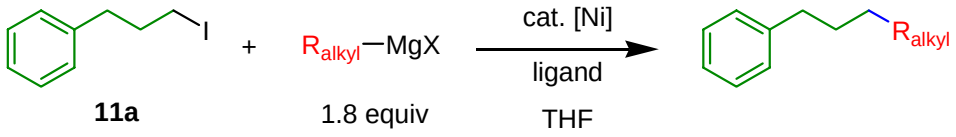
[109] Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525-1532.

[158] Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.

[135] Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646-5647.

[136] Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 6180-6182.

reagents (1.8 equiv). When $[Ni(py)_4Cl_2]$[141] was used as catalyst along with terpyridine or *sec*-Bu-pybox the substrate became unreacted. Even $Ni(cod)_2$ with terdentate ligands was inefficient. A higher yield was obtained by using commercially available $NiCl_2$[159] (5%) with TMEDA (*N*,*N*,*N'*,*N'*-tetramethyletylene diamine) (10%) in THF, both at -20 ºC and room temperature gives equivalent yield with varying in reaction time. At 25 ºC the reaction is faster and completes in only 15 minutes (**Table 9**, entry 5).



11a 1.8 equiv

Table 9. *Optimization of the conditions for alkyl–alkyl cross-coupling reactions*[a]

Entry	Catalyst (5%)	Ligand (10%)	R_{alkyl}	Temp. (ºC)	time (h)	Yield (%)
1	$Ni(py)_4Cl_2$	terpyridine	EtMgBr	-30	24	0
2		*sec*-Bu-Pybox	EtMgBr	-10	21	0
3[b]		terpyridine	Bn-MgCl	-10	27	0
4	$Ni(cod)_2$	*sec*-Bu-Pybox	*n*-BuMgCl	-10	24	0
5	**$NiCl_2$**	**TMEDA**	***n*-BuMgCl**	**25**	**0.25**	**75**
6	$NiCl_2$	TMEDA	*n*-BuMgCl	-20	3	75

[a]Conditions: $NiCl_2$ (5 mol %), TMEDA (10 mol %), 1.8 equiv. RMgX in THF at 25 ºC. [b]Reaction performed in anhydrous DMA.

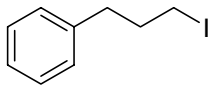
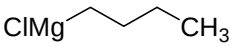
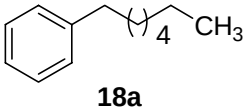
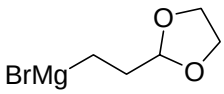
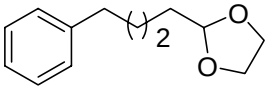
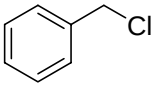
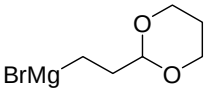
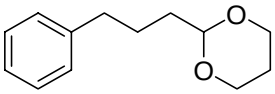
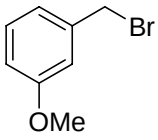
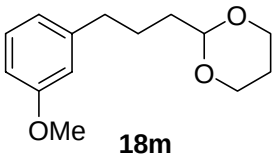
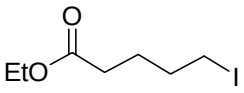
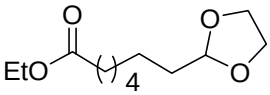
Primary alkyl iodides efficiently cross-coupled with primary alkylmagnesium reagents at room temperature. **Table 10** shows the Kumada cross-coupling results in high yield at room temperature. Benzylic halides **11l** and **11m** gave cross-coupling

[141] (a) Long, G. J.; Clarke, P. J. *Inorg. Chem.* **1978**, *17*, 1394-1401. (b) Bachman, R. E.; Whitmire, K. H.; Mandal, S.; Bharadwaj, P. K. *Acta Crystallogr. Sect. C* **1992**, *C48*, 1836-1837.

[159] Nickel (II) chloride, anhydrous powder (99.99%): Aldrich, ref. 451193.

product in lower yield. Primary alkyl group bearing ester group **11n** cross coupled in considerable yield of 42%.

Table 10. *Cross-coupling of primary alkyl iodides with alkylmagnesium reagents*

Entry	Substrate	RMgX	Product	Time (h)	Yield (%)
1	 **11a**	 **17a**	 **18a**	2	75
2	**11a**	 **17b**	 **12a**	7	80
3	 **11l**	 **17c**	 **18l**	2	31
4	 **11m**	**17c**	 **18m**	2	41
5	 **11n**	**17c**	 **18n**	3	43

Some other examples and the compatibility of the Grignard reagents with organic halides containing functional groups are under current investigation.

III. Nickel-catalyzed cascade formation of $C(sp^3)$–$C(sp^3)$ bonds by cyclization and cross-coupling reactions of iodoalkanes with alkylzinc and alkylmagnesium halides

IIIa. Nickel-catalyzed cyclization and cross-coupling reactions of iodoalkanes with alkylzinc bromides

The first report on a general and functional group tolerant alkyl−alkyl coupling reactions was published by Knochel using di(alkyl)zinc reagents and alkyl iodides in a Ni-catalyzed process, an achievement which constituted a milestone in this type of transformations.[32] Di(alkyl)zinc derivatives have been extensively used as nucleophiles in many reactions, including cross couplings for the formation of other types of C−C bonds.[119,158]

In subsequent studies the reaction was extended to the alkyl halides containing remote unsaturation (double bond, carbonyl group, cyano group), which facilitates its cross-coupling reaction with various diorganozincs in the presence of $Ni(acac)_2$ (7.5-10 mol % in THF/NMP mixtures).[121] Recently, Fu has reported Ni-catalyzed alkyl−alkyl couplings of alkylzinc halides with secondary iodides and bromides.[124,126] The use of optically active pybox-based ligands has allowed developing the first method that achieves catalytic asymmetric cross-coupling of alkyl electrophiles.[125] Alkyl−alkyl Negishi cross-couplings can be also catalyzed by Pd complexes when using heterocyclic carbene ligands.[68]

On the other hand, the Ueno-Stork reaction (radical cyclization of alkene containing haloketals) has been widely used for the formation of five-member cycles.[160]

---

[32] The first alkyl−alkyl coupling was reported by Suzuki by a Pd-catalyzed reaction of an alkylborane with an alkyl iodide: Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691-694.

[119] Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1996**, *34*, 2723-2725.

[158] Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.

[121] Giovannini, R.; Stüdemnann, N.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390.

[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

[126] Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483.

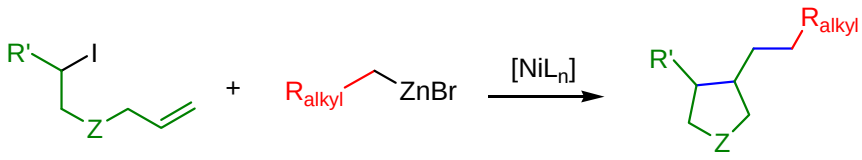
[125] Fisher, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595.

[68] Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805-3807.

[160] (a) Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566-1577. (b) Salom-Roig, X. J.; Denes, F.; Renaud, P. *Synthesis* **2004**, 1903-1928.

This reaction follows a radical mechanism and requires the use of a radical initiator in stoichiometric amount. We reasoned that radical chemistry from alkyl iodides triggered by Ni complexes could give rise to transformations involving the formation of several alkyl−alkyl bonds in a single operation in which 5-hexenyl radicals would experiment cyclization.[161]

In this chapter, we report the Ni-catalyzed sequential radical cyclization of alkyl halides containing an alkene group, followed by subsequent cross-coupling with alkylzinc bromides (**Scheme 19**). This reaction provides a new methodology of multiple bond formation in single operation. Experiments and calculations aimed to get insight into the mechanism have been also performed.



Scheme 19

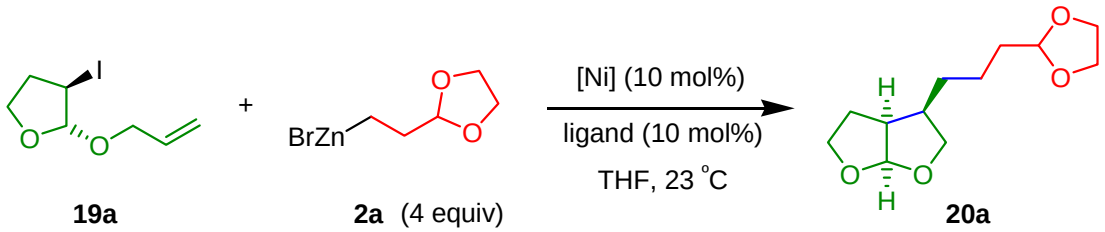
For the optimization of reaction conditions to afford alkyl−alkyl cross-coupling reaction, we first studied the reaction of iodoketal **19a** (which can be easily prepared by reaction of 2,3-dihydrofuran with the suitable allylic alcohol and NIS (*N*-iodosuccinimide) according to the described procedure),[162] with commercially available organozinc **2a** (4 equiv). In the conditions described by Vicic[127] (terpyridine, and $Ni(cod)_2$ as the catalytic system) the cyclization and coupling derivative **20a** was isolated in 24% yield as a single diasteroeomer (**Table 11**, entry 1). By using bipyridine, the yield was even lower (19%, **Table 11**, entry 2). Other Ni precursors ($NiBr_2$, $Ni(acac)_2$, $NiCl_2$) gave poorer results. When complex $[Ni(py)_4Cl_2]$[141] was used as catalyst along with terpyridine a higher yield was observed (57%, **Table 11**, entry 3).

[161] Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059-6064.

[162] Middelton, D. S.; Simpkins, N. S. *Synth. Commun.* **1989**, *19*, 21-29.

[127] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100-8101.

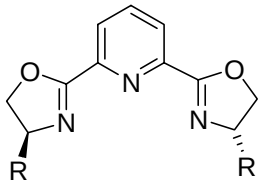
[141] (a) Long, G. J.; Clarke, P. J. *Inorg. Chem.* **1978**, *17*, 1394-1401. (b) Bachman, R. E.; Whitmire, K. H.; Mandal, S.; Bharadwaj, P. K. *Acta Crystallogr. Sect. C* **1992**, *C48*, 1836-1837.



19a **2a** (4 equiv) **20a**

Table 11. *Optimization of the reaction conditions by screening of ligands*

Entry	Catalyst	Ligand	t (h)	Yield (%)
1	$Ni(cod)_2$	Terpyridine	48	24
2		Bipyridine	48	19
3	$Ni(py)_4Cl_2$	Terpyridine	27	57
4		*i*-Pr-Pybox	12	61
5		*t*-Bu-Pybox	14	34
6		Ph-Pybox	15	38
7	**$Ni(py)_4Cl_2$**	***s*-Bu-Pybox**	**7**	**79**



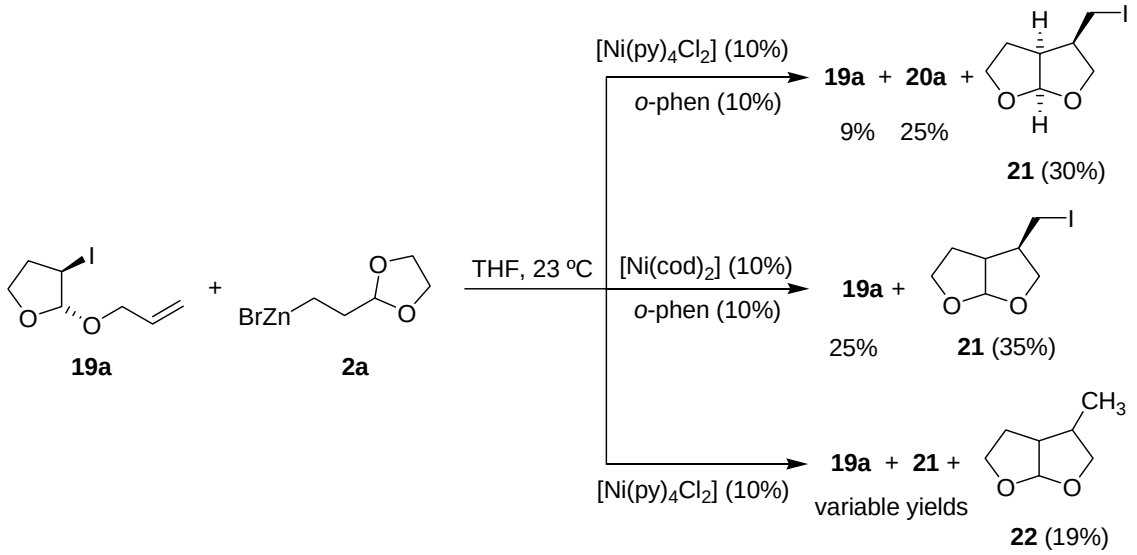
(*S*)-R-Pybox

R = *i*-Pr, *sec*-Bu, *t*-Bu, Ph

We tried some other nitrogen-based terdentate ligands based on the pybox skeleton. The di-*sec*-butyl derivative gave the best results, according to what had been previously observed by Fu in simple cross-couplings.[124] Homocoupling compound derived from the alkylzinc bromide was isolated in *ca*. 10% yield (in relation to the starting nucleophile) in most cases. The use of small amounts of the nucleophile led to lower yields.

The effect of some other ligands was also explored. Thus, in the presence of $Ni(py)_4Cl_2$/*o*-phenanthroline, rearranged derivative **21** was obtained in 30% yield along with required product **20a** in 25% yield (**Scheme 20**).

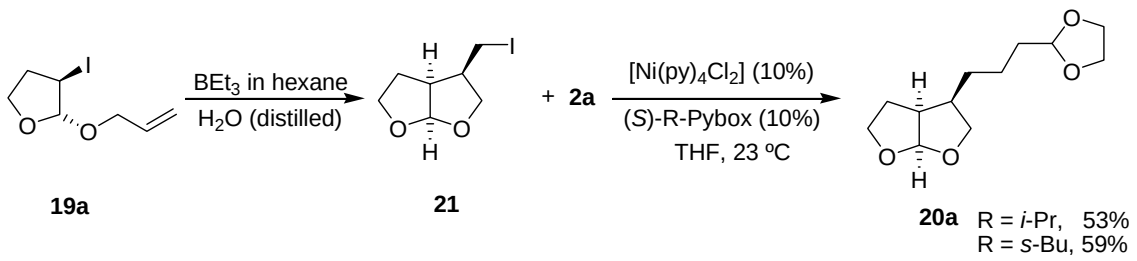
[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.



Scheme 20

Formation of this compound **21** further supports a radical mechanism, since the reaction of **19a** with BEt_3 has been reported to give **21**.[163] While by using $Ni(cod)_2$/*o*-phenanthroline, 25% yield of **19a** was obtained along with 35% of **21** (**Scheme 20**). In the absence of added ligands, a mixture of **19a**, **21**, and reduced **22** (probably formed by hydrogen abstraction from the solvent) was observed in moderate overall yield.

Compound **21** cannot be discarded as a reaction intermediate in the formation of **20a**, since the relative yield to **21** (in the reaction without added ligand) depends on the addition rate of the nucleophile. In fact, isolated **21** afforded the coupling product when subjected to the reaction conditions (**Scheme 21**).



Scheme 21

[163] (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604-8605. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041-11047.

The cyclization and cross-coupling reaction is general and can be extended to a wide variety of substrates holding different functional groups. Thus, compound **19a** gave good results with other organozinc reagents (**Table 12**, entries 2, and 3), affording only one diastereomer.

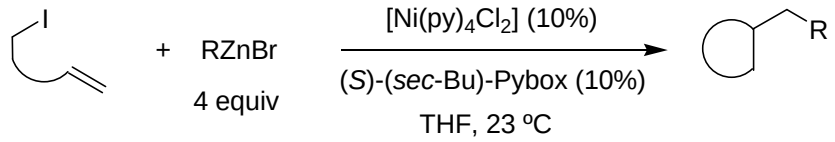
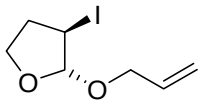
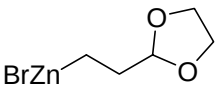
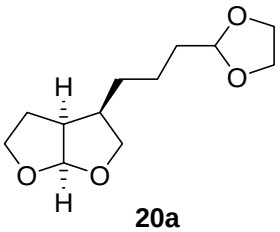
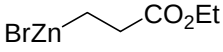
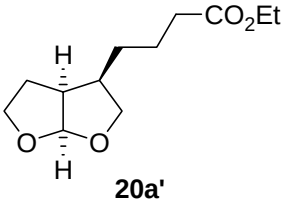
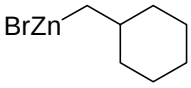
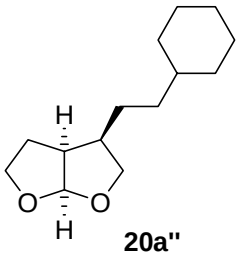
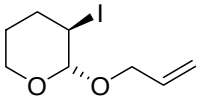
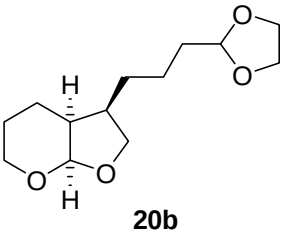
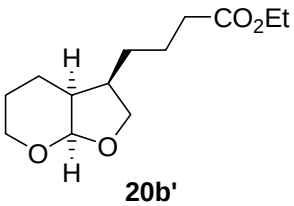
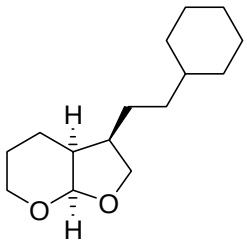
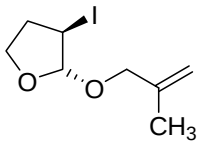
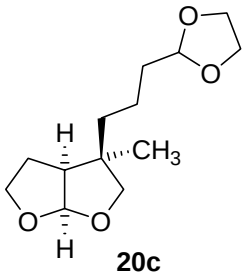
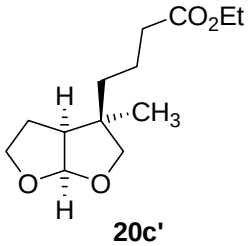
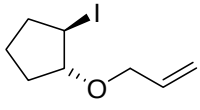
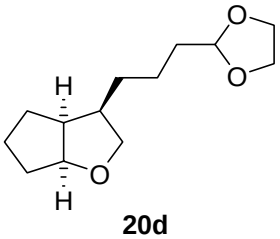
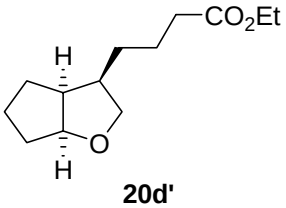
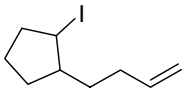
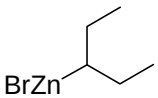
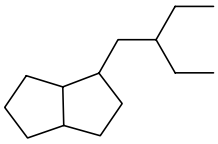


Table 12. *Ni-catalyzed formation of two alkyl−akyl bonds by radical cyclization and Negishi cross-coupling*

Entry	Substrate	RZnBr	Product	t (h)	Yield (%)
1	 **19a**	 **2a**	 **20a**	7	79
2	**19a**	 **2d**	 **20a'**	13	65
3	**19a**	 **2c**	 **20a''**	15	60
4[a]	 **19b**	**2a**	 **20b**	8	83 (92:8)
5[a]	**19b**	**2d**	 **20b'**	16	94 (97:3)

6[a]	**19b**	**2c**	 **20b''**	8	81 (93:7)
7	 **19c**	**2a**	 **20c**	8	64
8	**19c**	**2d**	 **20c'**	15	68
9[b,c]	 **19d**	**2a**	 **20d**	9	76 (64:36)
10[b,c]	**19d**	**2d**	 **20d'**	13	81 (57:43)
11[d]	 **19e**	 **2e**	 **20e**	24	73

[a]Measured by GC-MS. The minor isomer shows the opposite configuration in C3. [b]The relative configuration shown corresponds to the major isomer. The minor one is the epimer in C3. [c]Isomers were separated by flash chromatography. [d]Mixture of non-seperable diastereomers.

Six-member ring derivative **19b** gave better yields in the reactions with several alkylzinc bromides, although minor diastereomers of the main compounds were observed in the ^{1}H NMR spectra. Stereoisomers could not be separated by column

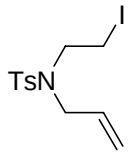
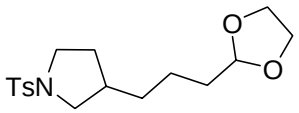
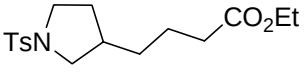
chromatography, but were characterized by GC-MS. Five-member iodoketal **19c** (**Table 12**, entries 7, and 8) yielded again only one stereoisomer. Instead, reaction of ether **19d** was not stereoselective (**Table 12**, entries 9, and 10) and the two possible epimers in C-3 were obtained in roughly equimolar amount. Therefore it is clear that in case of haloacetals, the size of the ring influenced on the stereochemical outcome as demonstrated by comparing entries 1-3, and 7, 8 with entries 4-6 (**Table 12**).

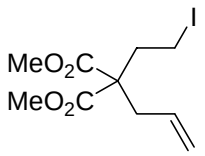
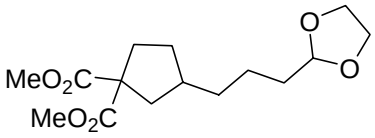
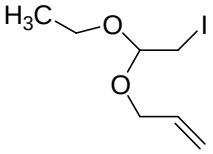
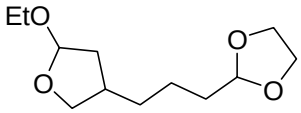
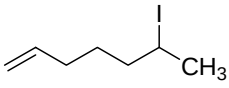
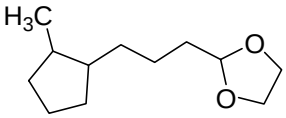
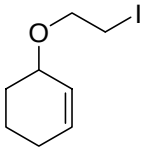
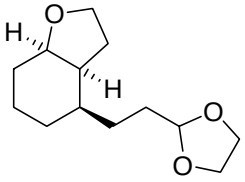
Iodoalkane containing a double bond without any heteroatom in the substrate and neither in the alkylzinc reagent also showed efficient cross-coupling, forming two alkyl−alkyl bonds by cyclization and intermolecular cross-coupling reaction (**Table 12**, entry 11).

Substrate **23a** showed interesting results, opening further applications for the synthesis of compounds containing the pyrrolidine ring (**Table 13**, entries 1, and 2). Malonate derivative **23b** also gave the expected compound although some direct coupling product without cyclization was obtained (13%).

Iodoacetal **23c**, which was prepared by treatment of a mixture of corresponding ethylvinyl ether and allyl alcohol with NIS, led to the expected product in moderate yield. Open chain iodoalkane **23d** gave a nonseperable mixture of expected product and a coupling derivative (**Table 13**, entry 5). Exocyclic ether **23e** was less prone to cyclization and the expected product was obtained in 46% yield along with the derivative resulting from cross-coupling of the iodoalkene with the zinc reagent without previous cyclization (36%).

Table 13. *Ni-catalyzed formation of two alkyl−akyl bonds by radical cyclization and Negishi cross-coupling*

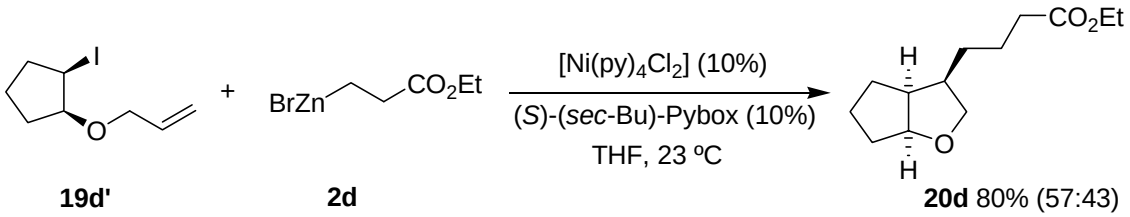
Entry	Substrate	RZnBr	Product	t (h)	Yield (%)
1	 **23a**	**2a**	 **24a**	16	83
2	**23a**	**2d**	 **24a'**	19	66

3[a]	 **23b**		**2a**	 **24b**	7	63
4	 **23c**		**2a**	 **24c**	7	55
5[b]	 **23d**		**2a**	 **24d**	11	84
6[c]	 **23e**		**2a**	 **24e**	11	46

[a]Coupling product without cyclization is formed in 13% yield (both compounds could not be separated). Yields are calculated from the ^{1}H NMR spectrum of the mixture). [b]Coupling product without cyclization is formed in 29% yield (yields are calculated from the ^{1}H NMR spectrum of the mixture). [c]Coupling product without cyclization is formed in 36% yield (isolated yield).

Mechanistic aspects

Experiments and calculations were performed to obtain mechanistic information about this reaction. The reaction of the *cis* stereoisomer of **19d** (**19d'**) in the standard reaction conditions led to **20d** (**Scheme 22**) with the same yield and steroselectivity than the product obtained from **19d**, indicating the presence of common reaction intermediate for both isomers, presumably the same secondary radical.

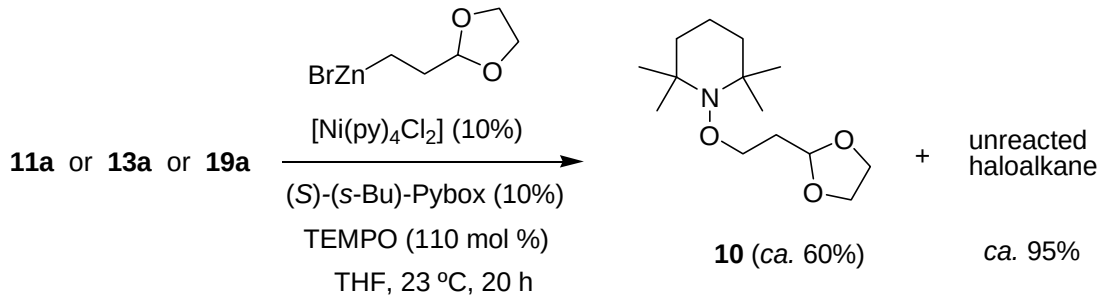


19d' **2d** **20d** 80% (57:43)

Scheme 22

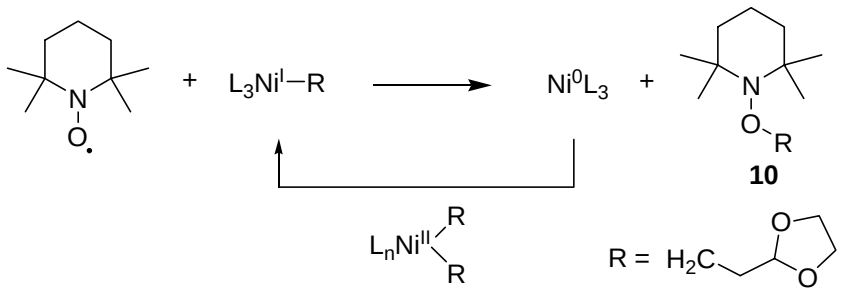
In the presence of BHT the reaction led to similar yields for simple cross-couplings of alkyl iodides **11a** and **13a** (65 and 72%, respectively). Instead, partial inhibition was observed for the cascade reaction of **19a**. Yields were variable, indicating partial inhibition, but non reproducible, and products resulting from the H atom transfer to putative intermediate radical (for example, compound **22**) were not detected.

On the other hand, when the reaction was performed in the presence of 1.1 equiv of the radical inhibitor TEMPO formal coupling product of this reagent with the radical derived from **2a** was obtained, along with unreacted haloalkane (**Scheme 23**).



Scheme 23

A plausible mechanism for this transformation is shown below (**Scheme 24**). TEMPO radical may react with the radical alkyl-Ni^{I} complex formed by transmetalation with the organozinc leading to the product and Ni(0). As previously proposed,[129] comproportion with a dialkyl-Ni^{II} derivative would regenerate the active catalyst.

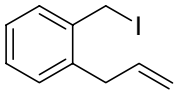
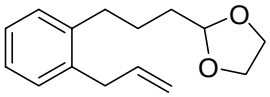
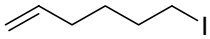
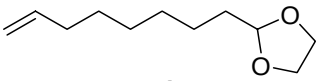
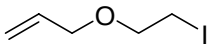
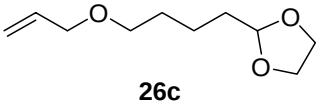
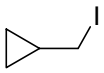
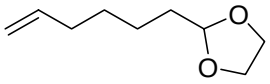


Scheme 24

[129] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

The competition between cross-coupling reactions with or without previous cyclization in some cases (**Table 13**, entries 3, 5, and 6), along with the plausible radical nature of the intermediate species led us to explore the coupling reactions of several radical clocks.[164] The results are summarized in **Table 14**.

Table 14. *Ni-Catalyzed cross-couplings of radical clock precursors with RZnBr ([Ni(py)$_4$Cl$_2$] (10 mol %), (S)-(sec-Bu)-pybox (10 mol%), THF, 23 ºC)*

Entry	Substrate	RZnBr	Product	k (s^{-1})[a]	t (h)	yield (%)
1	 **25a**	**2a**	 **26a**	0.1	3	82
2[b]	 **25b**		 **26b**	2.3×10^5	20	41
3[b]	 **25c**		 **26c**	9×10^6	11	25
4	 **25d**		 **26d**	6.7×10^7	5	63
5		**2b**	 **26d'**	6.7×10^7	4	59

[a]Cyclization rate for the radical formed from **25a-d** after homolytic C–I cleavage. [b]The low yields are probable due to the formation of volatile compounds resulting from hydrogen abstraction from the solvent.

Taking into account the cyclization (**Table 14**, entries 1-3) or ring-opening (**Table 14**, entries 4-5) rates for the radicals generated from the corresponding iodides, it can be derived that the key C–C coupling has a rate comparable to a unimolecular reaction taking place in the range $0.9\ 10^7$-$6.7\ 10^7\ s^{-1}$. Since a bimolecular process

[164] Newcomb, M., *Radicals in Organic Synthesis*, (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, Vol. 1, chapter 3.1, pp 317-336.

actually takes place, the intrinsic reactivity of the intermediate species must be even higher. Therefore, the formation of the C–C is not the rate limiting step.

The electron structure of alkyl-Ni^{I} terpyridine complexes, which has been proposed as the actual catalysts, had been previously calculated.[129] Although for the reaction of **19a** it became apparent that (*S*)-(*sec*-Bu)-pybox was the best ligand (79% yield), the reaction of **13a** with **2a** in the presence of terpyridine afforded **17a** in 63% yield, thus being this ligand as effective as (*S*)-(*sec*-Bu)-pybox (69% yield). This prompted us to calculate the structure of model complex methyl-Ni^{I} complex containing Me-pybox for the sake of comparison. Optimization at DFT level (see *Computational section* for details, p 268) shows a square-planar structure, typical of Ni^{II} complexes, with the single-occupied molecular orbital delocalized on the ligand, as previously reported for the terpyridine analogous complex (**figure 1**). Therefore, no special electronic differences have been found, and complex **XI** is better described as a Ni^{II} complex with a coordinated anionic terdentate ligand.[165]

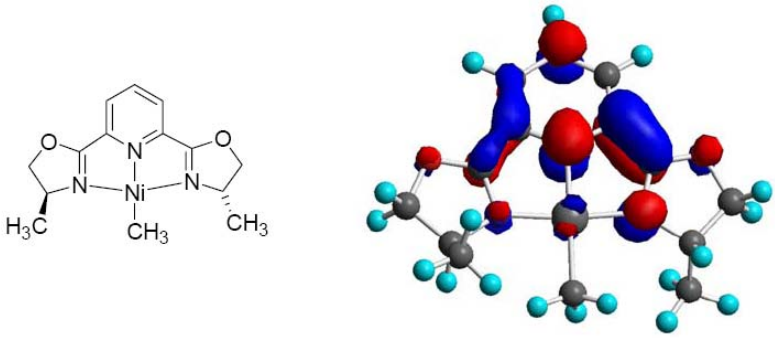


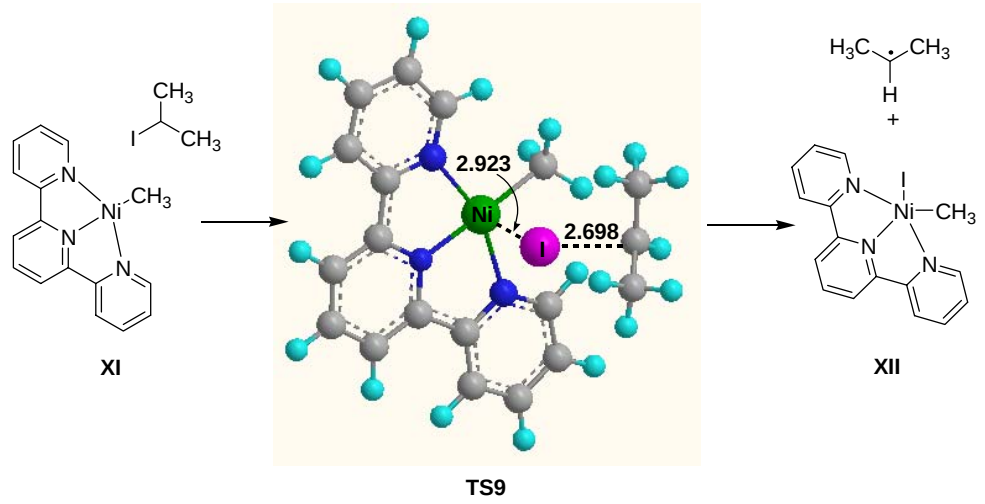
Figure 1. *Complex* **(Me-pybox)NiMe** *showing the ligand-centered single occupied molecular orbital.*

We have performed calculations to get insight into the formation of radicals from Ni^{I} complexes (see *Computational section* for details, p. 267). As model, methyl-Ni^{I} complex **XI** containing terpyridine was chosen. Simultaneously Phillips *et al.* also

[129] Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175-13183.

[165] Ni^{I} complexes prefer tetrahedral geometry around metal. For Ni(I) stabilization, see: (a) Dietrich-Buchecker, C.; Sauvage, J.-P.; Kern, J.-M. *J. Am. Chem. Soc.* **1989**, *111*, 7791-7800. (b) Dietrich-Buchecker, C.; Guilhem, J.; Kern, J.-M.; Pascard, C.; Sauvage J.-P. *Inorg. Chem.* **1994**, *33*, 3498-3502.

performed DFT calculations to examine the potential energy surfaces of Ni(I)-catalyzed Negishi alkyl–alkyl cross-coupling reactions by using propyl iodide and isopropyl iodide as model alkyl electrophiles and CH_3ZnI as a model alkyl nucleophile.[130] As it has been mentioned above, this species was shown by Vicic to be better described as a square-planar Ni^{II} coordinated to a monoelectronically reduced terpy ligand. We have located a transition state for the reaction of **XI** with 2-iodopropane. The process takes place with an activation free energy of only 5.1 kcal mol^{-1} starting from an association complex in which the iodide interacts with the Ni atom along the axis perpendicular to the coordination plane at 3.53 Å.[166] The reaction is exoergic (-7.3 kcal mol^{-1}) and affords the free radical and square-pyramidal Ni^{II} complex **XII** (**Scheme 25**). Although the calculation level does not allow fully quantitative conclusions, the activation energy is in accord with a reaction taking place at room temperature. The transition state shows a long C–I bond (2.698 Å, compare with 2.250 Å for 2-iodopropane at the same level of calculation), corresponding to a relatively late transition state.



Activation free energy of 5.1 kcal mol^{-1}, the reaction is exoergic (-7.3 kcal mol^{-1}). Scheme includes the geometry of the **TS9***, in which specified distances are in Å.*

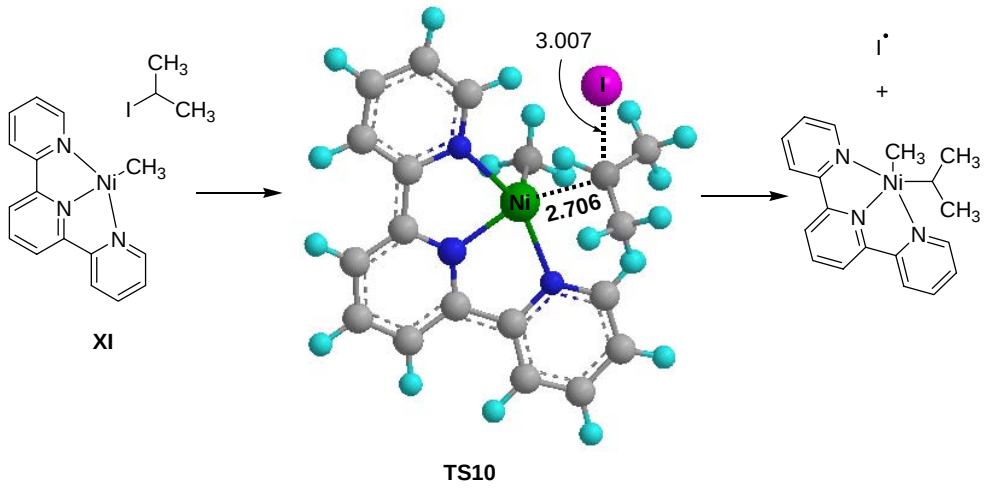
Scheme 25

We have also calculated the transition state for the reaction of **XI** with 2-iodopropane to give radical iodo and a dialkyl-Ni^{II} complex containing methyl and

[130] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680-3688.

[166] This association complex has been obtained by optimization after partial intrinsic reaction coordinate (IRC) calculation (15 cycles with the default Gaussian03 IRC parameters).

isopropyl as carbon ligands (**Scheme 26**), which would presumably evolve by reductive elimination. This transition state is 10.2 kcal mol^{-1} less stable than **TS9**, and therefore this alternative can be discarded.

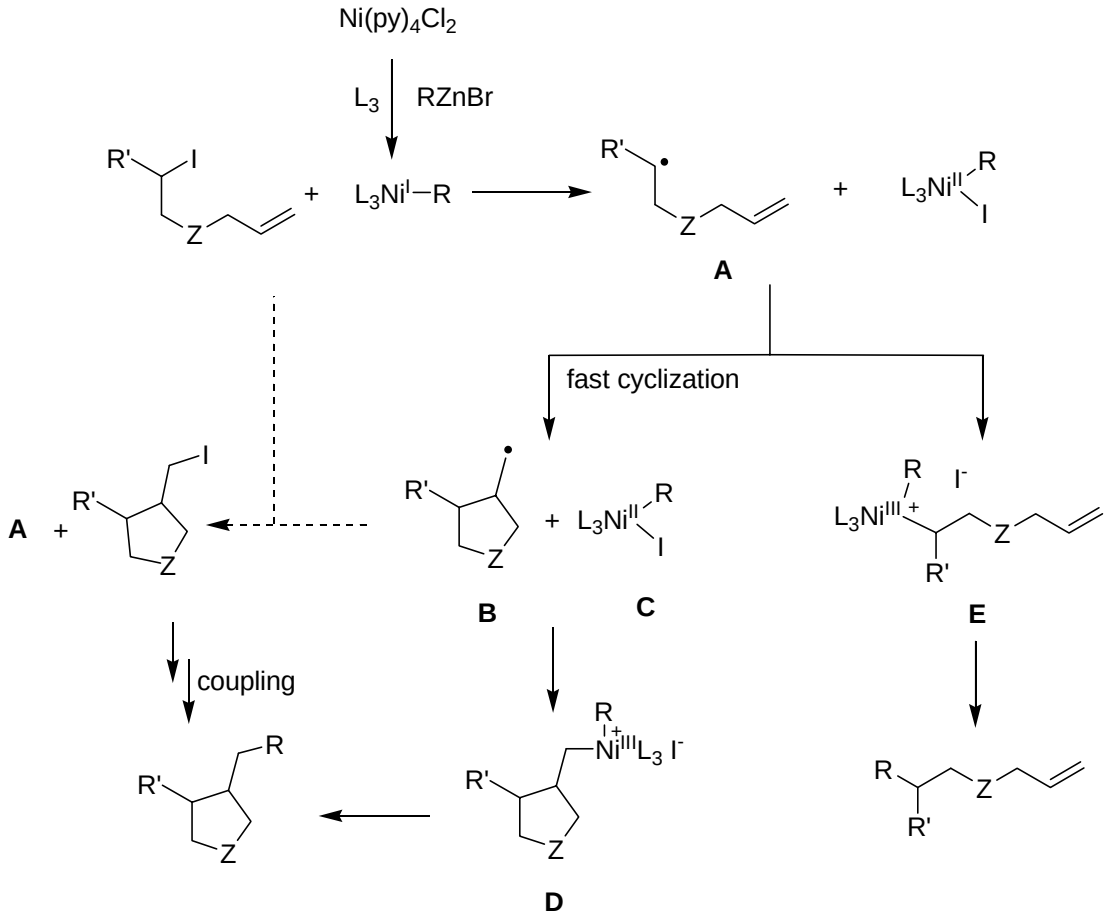


TS10 *is 10.2 kcal* mol^{-1} *less stable than* **TS9**. *Scheme includes the geometry of the* **TS10**, *in which specified distances are in Å.*

Scheme 26

A plausible mechanism is shown in **Scheme 27**. Our experimental and computational results, which are in accord with the previous proposal for simple couplings, suggest that free radicals (**A**) are readily formed from alkyl iodides, and that they last long enough to cyclize to intermediates **B** in some cases. If cyclization is slow, a faster coordination to Ni^{II} complex to give dialkyl-Ni^{III} intermediates **E** would take place. Ni^{III} complex would evolve by reductive elimination to give the coupling product and regenerating the Ni^{I} active species. The effect of BHT is not clear, since it only prevents the reaction of **19a** but not simple cross-couplings. Since reduced products (such as **22**) have not been detected in the reaction of **1a** in the presence of BHT, our hypothesis is that this reagent decomposes intermediate Ni^{II} complexes **C** when the radical takes time to cyclize instead of rapidly coordinating to Ni.

Alternatively, radical **B** could react with the starting iodide to give rearranged compounds such as **21**, which would subsequently couple to the organozinc reagent to afford the coupling product.



Scheme 27

According to experimental evidences and computational results, it seems reaction follows radical pathway. Ni^{I}-alkyl is the main active species involved to initiate the reaction, so it is assumed that reaction follows Ni^{I}-Ni^{III} catalytic cycle.

IIIb. Nickel-catalyzed cyclization and cross-coupling reactions of iodoalkanes with alkylmagnesium halides

More than half a century ago, Kharasch and co-workers investigated the effect of transition metal salts such as iron and cobalt in reactions between organic halides and Grignard reagents.[2] The reaction was virtually uncontrollable because the mixture of homo-coupling, disproportionation, and cross-coupling of alkyl groups from the

[2] (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320; (b) Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 504-507; (c) Cotton, F. A. *Chem. Rev.* **1955**, *55*, 551-594.

combination of the alkyl Grignard reagent and the alkyl halide was observed. Later, Kochi and coworkers reported selective cross-coupling reactions under copper and iron catalysis conditions.[4] Little attention had also been paid to iron and cobalt since Kochi's findings. Recently Fürstner and co-workers have reported that ligandless iron salts function as catalysts in cross-coupling reactions between aryl chlorides and alkyl Grignard reagents.[167] Nakamura and co-workers[168] and Hayashi and Nagano[169] have also developed cross-coupling reactions with iron catalysis, in which primary and secondary alkyl halides are usable as coupling partners for aryl Grignard reagents.

Radical reaction mediated by tin hydrides, has been extensively investigated and widely used in organic synthesis. The most attractive feature of this strategy is the generation of a new carbon-metal bond by the capture of a carbon-centered radical, derived from a certain radical transformation, with a metallic reagent. Sequential ionic reaction offers multi-bond formation process. However, further C–C bond formation is not always easy because of the low stability or reactivity of the resulting organometallics. Electrophiles used for elongating a carbon chain are allyl halides and reactive carbonyl compounds such as acid chloride, aldehyde, and ketone. In a few cases, activated carbon-carbon multiple bonds[65c] and alkyl halides[170] could be employed as electrophiles. On the other hand, Ueno-Stork reaction, a radical cyclization of alkene containing haloketals has been widely used for the formation of five-member cycles.[154]

Related Co-catalyzed radical cyclizations of olefin containing haloacetals followed by coupling with Grignard reagents have been developed by

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[4] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1483-1487. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351-360.

[167] Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609-612.

[168] Nakamura, M.; Matsuo K.; Ito, K.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686-3687.

[169] Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297-1299.

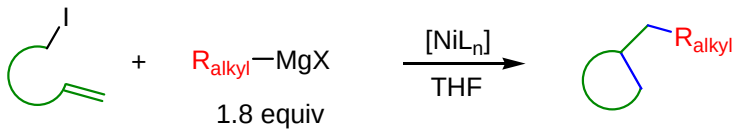
[65c] Stadtmüller, H.; Vapuel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204-1220.

[170] (a) Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 11822-11823. (b) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291-5297.

[154] (a) Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566-1577. (b) Salom-Roig, X. J.; Denes, F.; Renaud, P. *Synthesis* **2004**, 1903-1928.

Oshima.[74a,b,f,171,172] Palladium-catalyzed cyclization and cross-coupling of acetylenic aryl triflates[173] and bromoenyne[174] with organotin reagents is also been reported

As per our knowledge there are not any reports available in case of Pd and Ni-catalyzed cyclization and cross-coupling reaction with alkylmagnesium reagents. Herein we wish to report first, easy and simple procedure for Ni-catalyzed cyclization and cross-coupling of iodoalkanes with alkylmagnesium reagents (**Scheme 28**).



Scheme 28

The optimized conditions for cross-coupling of alkyl halides with alkylmagnesium reagents (see, *Section IIb*) are also efficient to catalyze cyclization and cross-coupling procedure effectively. Iodoacetal **19a** gave good yields of desired product with alkylmagnesium halides, **3a** and **3b** (**Table 15**, entries 1 and 2). Substrate **23a** gave pyrrolidine ring derivative (**Table 15**, entry 3). Secondary iodoalkane containing a double bond in an open chain gave cyclized product in moderate yield (**Table 15**, entry 4). Iodoalkane bearing tertiary amine moiety gave expected products in high yield (entries 5 and 6).

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[74] (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374-5375. (b) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137-4139. (f) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886-1889.

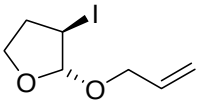
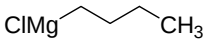
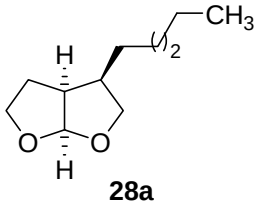
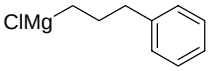
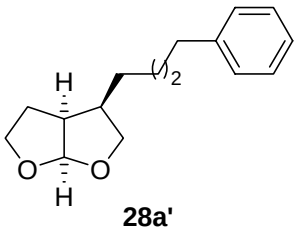
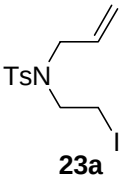
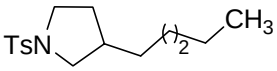
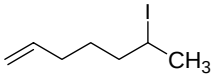
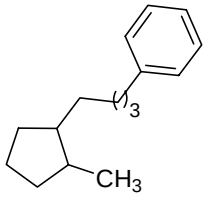
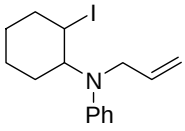
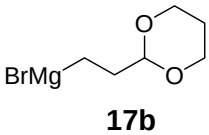
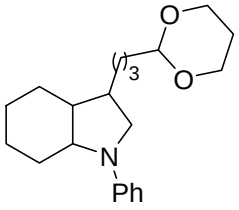
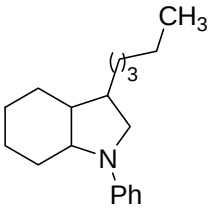
[171] (a) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565-1567. (b) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron*, **2007**, *63*, 8609-8618.

[172] Co-catalyzed Heck type reactions of alkyl halides: (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514-6515. (b) Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257-2259.

[173] Luo, F.; Wang, R. *Tetrahedron Lett.* **1991**, *32*, 7703-7706.

[174] Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323-2326.

Table 15. *Ni-catalyzed formation of two alkyl-akyl bonds by radical cyclization and cross-coupling of iodoalkanes with alkylmagnesium halides*

Entry	Substrate	R_{alkyl}–MgX	Product	t (h)	Yield (%)
1[a]	 **19a**	 **17a**	 **28a**	2	65
2	**19a**	 **17c**	 **28a'**	2	58
3[b]	 **23a**	**17a**	 **29a**	1	59
4[c]	 **27b**	**17c**	 **29b**	1	54
5	 **27c**	 **17b**	 **29c**	1	61
6	**27c**	**17a**	 **29c'**	1.5	73

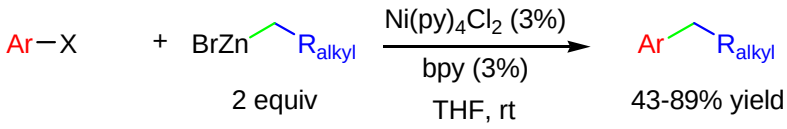
[a]Bromoacetal gave 31% yield of the desired product. [b]Cyclized and reduced product (3-methyl-1-tosylpyrrolidine), was obtained in 13% yield. [c]Mixture of two stereoisomers (nonseperable, in 70:30 proportions).

Current efforts are directed at further expanding the scope of Ni-catalyzed cyclization and cross-coupling of iodoalkanes with alkylmagnesium reagents and to study the mechanistic aspects of the same.

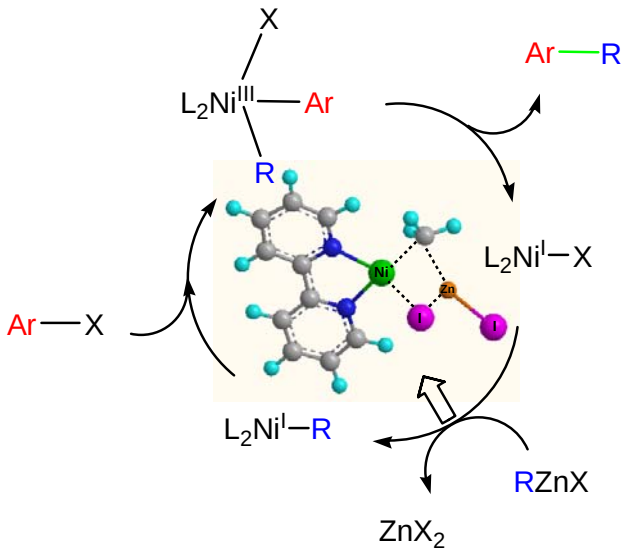
CONCLUSIONS

1. Ni-catalyzed convenient aryl-alkyl coupling

We have developed conditions for a general Ni-catalyzed Negishi cross-coupling of alkylzinc halides with aryl, heteroaryl and alkenyl halides taking place in smooth conditions, with a low catalyst loading, and in the presence of a wide variety of functional groups.

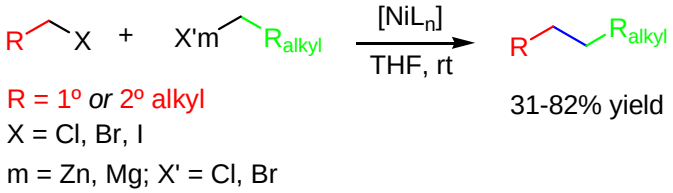


The reaction most probably takes place through Ni^{I}-Ni^{III} catalytic cycle, and involves a fast transmetalation from alkylzinc bromides to Ni^{I}, according to the experimental evidence and computational results. A transition state for the transmetalation of organozinc halides to Ni(I) has been located for the first time. Alternative oxidative addition of PhI to Ni(I) complexes is less favourable according to calculations. The key alkyl-Ni(I) intermediate Ni(bipy)Me has the unpaired electron located on the π–orbitals of the ligand, as it occurs for complexes containing tridentate nitrogen-based ligands (terpiridine and pybox derivatives).

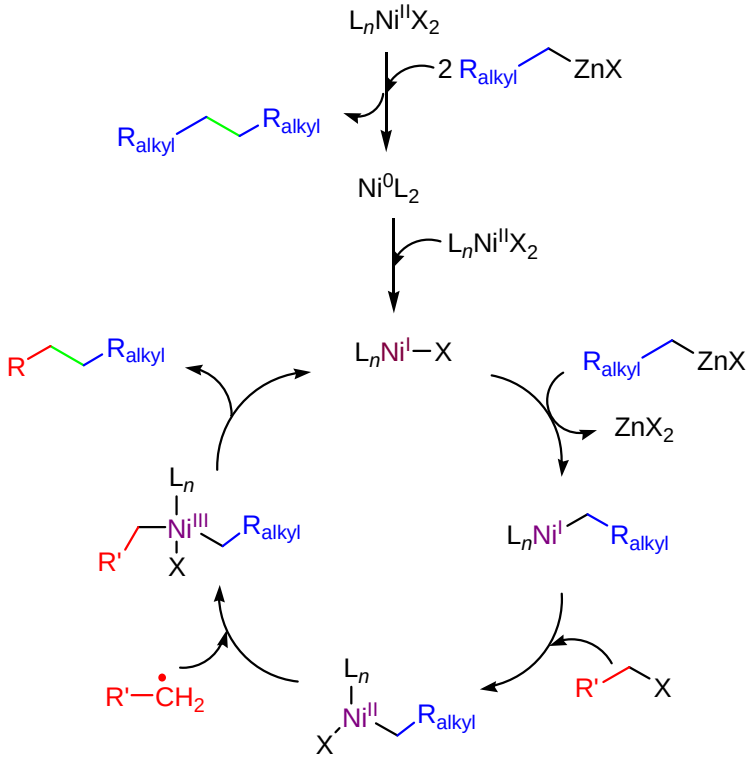


2. Ni-catalyzed alkyl-alkyl cross-coupling

We have developed nickel-catalyzed Negishi and Kumada type cross-coupling reactions of alkyl halides with alkylzinc and alkylmagnesium reagents under $Ni(py)_4Cl_2$/(*S*)-(*sec*-Bu)-pybox and $NiCl_2$/TMEDA catalysis, respectively.

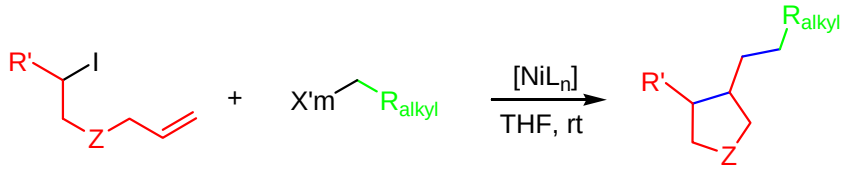


We have performed computational calculations for alkyl-Ni^I complex, which has been proposed as the actual catalyst. Reaction of alkyl halides with alkyl-Ni^I complex takes place by halogen abstraction to form a Ni(II) complex and an alkyl radical, which after faster coordination to Ni^{II} complex gives dialkyl-Ni^{III} intermediate. Ni^{III} complex evolve by reductive elimination to afford a cross-coupling product, regenerating Ni^I–X.



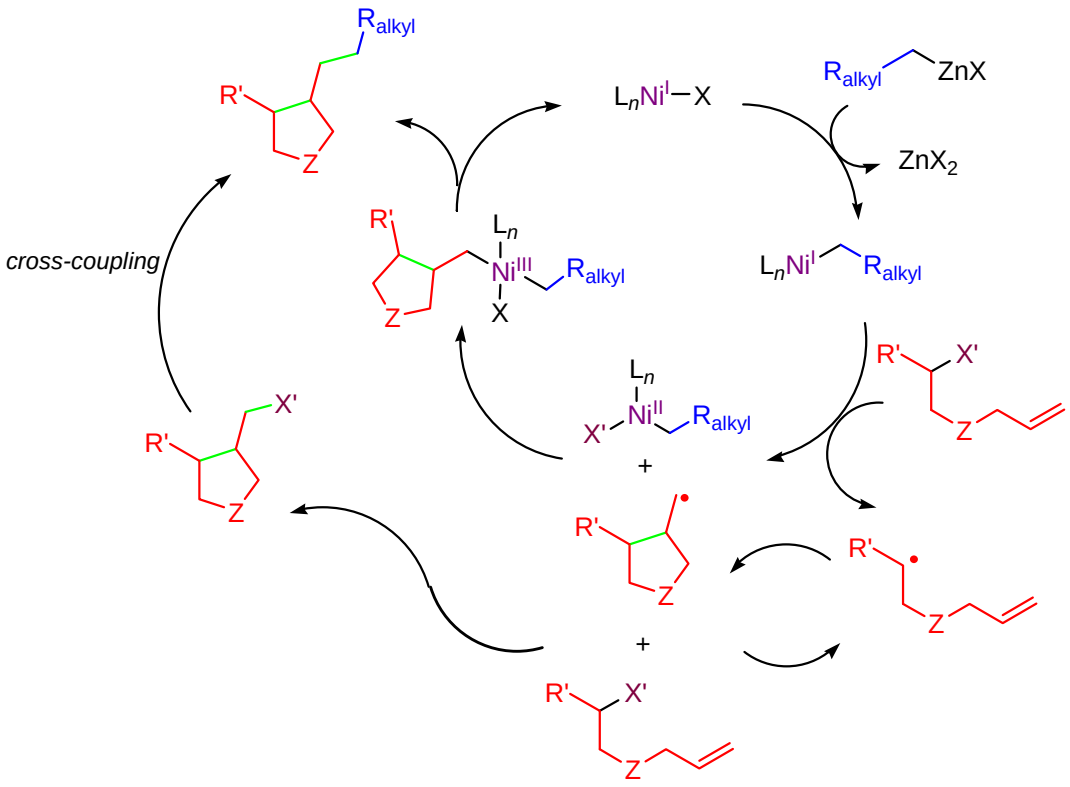
3. Ni-catalyzed cyclization/cross-coupling of iodoalkanes with alkylzinc and alkylmagnesium reagents

The formation of two $C(sp^3)$–$C(sp^3)$ bonds can be achieved in a single operation by sequential cyclization and cross-coupling of alkylzinc and alkylmagnesium halides with iodoalkanes containing an alkene group.



R' = H, alkyl
X = Br, I
m = Zn, Mg; X' = Cl, Br

Our calculations show that the reaction of alkyl-Ni^I complexes with iodoalkanes is fast and affords free radicals, in accord with the experimental observations. Furthermore cyclization of these radicals with alkenes forms cyclized compounds and coupling with alkylzinc or alkyl magnesium halides would afford the final products.



Additional efforts to expand the scope of Ni-catalyzed cross coupling as well as cyclization/cross-coupling reactions of alkyl electrophiles with alkylmagnesium reagents and its mechanistic study are underway.

EXPERIMENTAL SECTION

I. General materials and methods

All reactions were carried out under Ar under anhydrous conditions. Anhydrous and analytical grade THF, purchased from Carlo Erba reagents-SDS S. A., was refluxed over sodium and benzophenone as an indicator and distilled every time before using. Anhydrous and analytical grade CH_2Cl_2, purchased from Carlo Erba reagents-SDS S. A., was used after keeping it over activated 4Å molecular sieves.

Organozinc reagents and organomagnesium chlorides were purchased from Aldrich as 0.5 M solutions and 2.0 M solutions in THF, respectively, except (3-phenylpropyl)magnesium chloride (**17b**),[175] and [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide (**17c**) (at room temperature)[178] were prepared according to the literature procedure.

$NiCl_2$,[158] $Ni(cod)_2$ (Aldrich), 2,2′-bipyridyl (Fluka), 2,2′:6′,2″-terpyridine (Aldrich), *o*-phenanthroline monohydrate (Fluka) and TMEDA (Aldrich) were purchased. $[Ni(py)_4Cl_2]$[140] and *s*-Bu-Pybox[124] were prepared according to the literature procedure.

Thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck, TLC Silica gel 60 F_{254}). Chromatographic purifications were carried out using flash grade silica gel (Carlo Erba reagents-SDS S. A., Chromatogel 60 ACC, 40-60 μm).

NMR spectra were recorded at 23 °C on the following spectrometers: Bruker AC-300 (300 MHz in ^1H, and 75 MHz in ^{13}C) in deuterated chloroform with the solvent signal serving as internal standard at 7.26 ppm in ^1H and 77.4 ppm in ^{13}C NMR; and Bruker AMX-500 (500MHz in ^1H, 125 MHz in ^{13}C). The coupling constants (*J*) are reported in Hz and the chemical shifts (δ) in ppm.

Mass spectra (FAB, EI and Electrospray) were reported on a GCT Walters spectrometer coupled to a chromatogram of gases (model 6890N of a Agilent technologies).

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[175] Dahl, B. J.; Branchaud, B. P. *Tetrahedron Lett.* **2004**, *45*, 9599–9602

[158] Nickel (II) chloride, anhydrous powder (99.99%): Aldrich, ref. 451193

[140] (a) Long, G. J.; Clarke, P. J. *Inorg. Chem.* **1978**, *17*, 1394-1401. (b) Bachman, R. E.; Whitmire, K. H.; Mandal, S.; Bharadwaj, P. K. *Acta Crystallogr. Sect. C* **1992**, *C48*, 1836-1837.

[124] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

The usual extractive work-up refers to proportioning of the crude reaction between an organic solvent and water, phase seperation, drying (over anhydrous Na_2SO_4 or $MgSO_4$), and evaporation under reduced pressure.

II. Nickel catalyzed cross-coupling of C(sp^2) electrophiles with alkylzinc reagents

IIa. Materials, methods and optimization of the reaction conditions

The following reagents were purchased: 4-Iodoanisole (Aldrich), iodobenzene (Across Organics), 3-iodotoluene (Aldrich), 4-iodoaniline (Fluka), 4-iodobenzotrifluoride (Aldrich), 4-iodoacetophenone (Aldrich), 4-iodobenzonitrile (Aldrich), 4-bromobenzonitrile (Aldrich), 1-chloro-4-iodobenzene (Fluka), 1-bromo-3-iodobenzene (Aldrich), 4-bromobenzyl bromide (Aldrich), 4-bromobenzaldehyde (Aldrich), 2-iodobenzoic acid (Aldrich), 3-iodobenzoic acid (Fluka), 4-iodobenzoic acid (Aldrich), 2-iodophenylaceticacid (Aldrich), 2-iodopyridine (Aldrich), and 2-iodothiophene (Aldrich).

Compounds methyl 2-iodobenzoate (**1f-*o***), methyl 3-iodobenzoate (**1f-*m***), methyl 4-iodobenzoate (**1f-*p***),[176] 4-iodophenyl 4-methylbenzenesulfonate (**1l**),[177] 2-iodobenzaldehyde (**1o**),[178] (*E*)-1-iodohex-1-ene (**6a**),[179] (*E*)-(2-iodovinyl)cyclohexane (**6b**) and (*E*)-(2-iodovinyl)benzene (**6c**), [180] were prepared according to literature procedure.

General optimized procedure for the cross-coupling reactions of aryl, heteroaryl, and alkenyl halides with alkylzinc bromides:

A 25 mL flask was charged with $Ni(py)_4Cl_2$ (5.7 mg, 0.0128 mmol), bpy (1.9 mg, 0.0128 mmol) and a stir bar in air. The flask was sealed with a septum and backfilled with Ar. A solution of the aryl iodide (0.427 mmol) in dry THF (2 mL) was added via

[176] Dahl, B. J.; Branchaud, B. P. *Tetrahedron Lett.* **2004**, *45*, 9599–9602

[177] Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606–2612.

[178] Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T.; White, A. J. P. *Chem. Eur. J.* **2005**, *11*, 69-80.

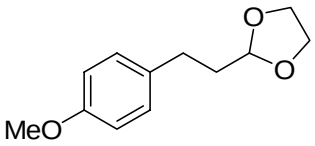
[179] Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.*, **1987**, *109*, 2138-2152.

[180] Auge, J.; Boucard, V.; Gil, R.; Lubin-Germain, N.; Picard, J.; Uziel, J. *Synth. Comm.* **2003**, *33*, 3733-3739.

syringe. After stirring for 3-4 min at rt, the corresponding alkylzinc bromide (0.5 M THF solution, 0.854 mmol) was added, and the reaction mixture was stirred at room temperature for the indicated time. The reaction mixture was then transferred with diethyl ether (20 mL) to a separatory funnel containing water (20 mL), the product was extracted with ether (2×30 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and concentrated and the residue was purified by silica gel column chromatography (Hexane: EtOAc).

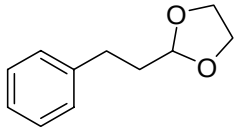
IIb. Experimental data

2-(4-Methoxyphenethyl)-1,3-dioxolane (**3a**)[142]



Following general procedure for cross-coupling, **3a** was obtained in 80% yield as a Colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.08 (m, 2H), 6.86-6.79 (m, 2H), 4.88 (t, *J* = 4.7 Hz, 1H), 4.03-3.84 (m, 4H), 3.78 (s, 3H), 2.70 (dd, *J* = 8.1, 4.7 Hz, 2H), 1.95 (ddd, *J* = 8.2, 5.6, 4.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 158.16 (C), 133.94 (C), 129.56 (2·CH), 114.13 (2·CH), 104.18 (CH), 65.23 (2·CH_2), 55.53 (CH_3), 36.07 (CH_2), 29.58 (CH_2).
TOF MS EI+: Calcd. for $C_{12}H_{16}O_3$: 208.1099; Found: 208.1109.

2-Phenethyl-[1,3]dioxolane (**3b**)[181]



Following general procedure for cross-coupling, **3b** was obtained in 78% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.14 (m, 5H), 4.90 (t, *J* = 4.8 Hz, 1H), 4.03-3.84 (m, 4H), 2.76 (dd, *J* = 8.1, 4.1 Hz, 2H), 1.99 (ddd, *J* = 9.9, 5.7, 4.7 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, DEPT-135)

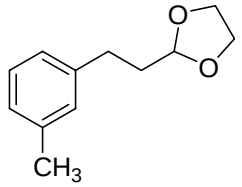
[142] Motoki, Y.; Fujita, S.; Fujihara, Y.; Okada, Y.; Nombra, M. *J. Oleo Sci.* **2003**, *9*, 495-498.

[181] Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575-578.

δ 141.96 (C), 128.74 (4·CH), 126.22 (CH), 104.21 (CH), 65.30 (2·CH_2), 35.87 (CH_2), 30.51 (CH_2).

TOF MS EI+: Calcd. for $C_{11}H_{14}O_2$: 178.0994; Found: 178.1004.

2-(3-Methylphenethyl)-1,3-dioxolane (**3c**):

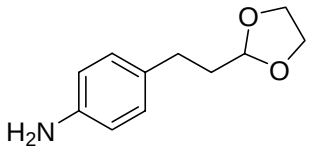


Following general procedure for cross-coupling, **3c** was obtained in 60% yield as a colourless oil (Hexane: EtOAc = 100:3 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.5 Hz, 1H), 7.06-6.97 (m, 3H), 4.90 (t, *J* = 4.7 Hz, 1H), 4.06-3.81 (m, 4H), 2.76-2.67 (m, 2H), 2.33 (s, 3H), 2.02-1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 141.5 (C), 133.9 (C), 129.2 (CH), 128.3 (CH), 126.6 (CH), 125.4 (CH), 103.9 (CH), 65.0 (2·CH_2), 35.5 (CH_2), 30.1 (CH_2), 21.4 (CH_3).

Electrospray (Na^+): Calcd. for $C_{12}H_{16}O_2$: 215.1042; Found: 215.1039.

Elemental Analysis: C, 74.97; H, 8.39; Found: C, 75.27; H, 8.49.

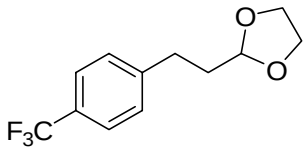
4-[2-(1,3-Dioxolan-2-yl)ethyl]benzenamine (**3d**)



Following general procedure for cross-coupling, **3d** was obtained in 46% yield as a reddish oily liquid (Hexane: EtOAc = 3:7 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03-6.96 (m, 2H), 6.65-6.59 (m, 2H), 4.87 (t, *J* = 4.9 Hz, 1H), 4.02-3.83 (m, 4H), 3.55 (br s, 2H), 2.65 (dd, *J* = 8.1, 4.5 Hz, 2H), 1.93 (ddd, *J* = 10.4, 5.6, 4.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 144.66 (C), 131.95 (C), 129.50 (2·CH), 115.65 (2·CH), 104.34 (CH), 65.26 (2·CH_2), 36.17 (CH_2), 29.69 (CH_2).

TOF MS EI+: Calcd. for $C_{11}H_{15}NO_2$: 193.1103; Found: 208.1107.

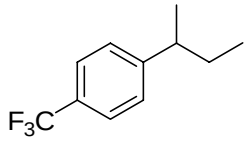
2-[4-(Trifluoromethyl)phenethyl]-1,3-dioxolane (**3e**)



Following general procedure for cross-coupling, **3e** was obtained in 69% yield as a colourless liquid (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.35-7.28 (m, 2H), 4.89 (t, J = 4.6 Hz, 1H), 4.03-3.84 (m, 4H), 2.85-2.77 (m, 2H), 1.99 (ddd, J = 8.2, 5.7, 4.5 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, DEPT-135) δ 146.18 (C), 146.17 (C), 129.08 (4·CH), 128.69 (q, C, J_{CF} = 32.3 Hz), 127.51 (q, C, J_{CF} = 272.1 Hz), 125.70 (q, C, J_{CF} = 3.8 Hz), 103.90 (CH), 65.40 (2·CH_2), 35.51 (CH_2), 30.27 (CH_2).

TOF MS EI+: Calcd. for $C_{12}H_{13}F_3O_2$: 246.0868; Found: 246.0876.

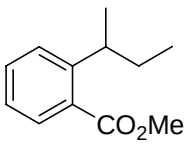
1-*sec*-Butyl-4-(trifluoromethyl)benzene (3e')



Following general procedure for cross-coupling, **3e'** was obtained in 58% yield as a colourless liquid (Hexane: EtOAc = 40:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.31-7.25 (m, 2H), 2.73-2.60 (m, 1H), 1.67-1.55 (m, 2H), 1.25 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 152.16 (C), 152.14 (C), 128.55 (q, C, J_{CF} = 32.3 Hz), 127.77 (4·CH), 125.59 (q, C, J_{CF} = 3.86 Hz), 124.82 (q, C, J_{CF} = 271.5 Hz), 42.10 (CH), 31.47 (CH_2), 22.00 (CH_3), 12.48 (CH_3).

TOF MS EI+: Calcd. for $C_{11}H_{13}F_3$: 202.0969; Found: 202.0979.

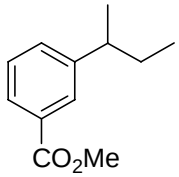
Methyl 2-*sec*-butylbenzoate [**3f-*o*** (*ortho*)**]**:



Following general procedure for cross-coupling, **3f-*o*** was obtained in 43% yield as a pale yellow oily liquid (Hexane: EtOAc = 100:5 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.68 (m, 1H), 7.49-7.41 (m, 1H), 7.38-7.33 (m, 1H), 7.25-7.17 (m,

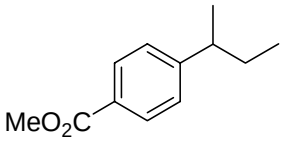
1H), 3.89 (s, 3H), 3.52-3.38 (m, 1H), 1.74-1.50 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 169.0 (C), 148.5 (C), 131.6 (CH), 130.6 (C), 129.6 (CH), 126.6 (CH), 125.3 (CH), 51.9 (CH_3), 36.4 (CH), 31.0 (CH_2), 21.7 (CH_3), 12.2 (CH_3).
TOF MS EI+: Calcd. for $C_{12}H_{16}O_2$: 192.1150; Found: 192.1159.

Methyl 3-*sec*-butylbenzoate [**3f-*m*** (*meta*)]:



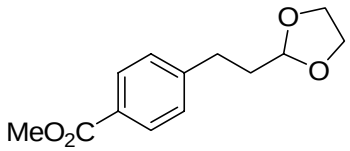
Following general procedure for cross-coupling, **3f-*m*** was obtained in 56% yield as a pale yellow oily liquid (Hexane: EtOAc = 100:5 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 2H), 7.40-7.32 (m, 2H), 3.91 (s, 3H), 2.72-2.60 (m, 1H), 1.62 (quint, J = 7.3 Hz, 2H), 1.26 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 167.4 (C), 148.0 (C), 131.8 (CH), 130.1 (C), 128.3 (CH), 128.2 (CH), 127.1 (CH), 52.0 (CH_3), 41.6 (CH), 31.0 (CH_2), 21.7 (CH_3), 12.1 (CH_3).
TOF MS EI+: Calcd. for $C_{12}H_{16}O_2$: 192.1150; Found: 192.1155.

Methyl 4-*sec*-butylbenzoate [**3f-*p*** (*para*)]:



Following general procedure for cross-coupling, **3f-*p*** was obtained in 60% yield as a pale yellow oily liquid (Hexane: EtOAc = 100:5 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.93 (m, 2H), 7.27-7.22 (m, 2H), 3.90 (s, 3H), 2.72-2.60 (m, 1H), 1.61 (quint, J = 7.3 Hz, 2H), 1.25 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 167.2 (C), 153.2 (C), 129.7 (2·CH), 127.8 (C), 127.1 (2·CH), 51.9 (CH_3), 41.8 (CH), 30.9 (CH_2), 21.6 (CH_3), 12.1 (CH_3).
TOF MS EI+: Calcd. for $C_{12}H_{16}O_2$: 192.1150; Found: 192.1150.

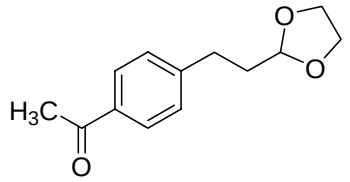
Methyl 4-[2-(1,3-dioxolan-2-yl)ethyl]benzoate (**3f'**)



Following general procedure for cross-coupling, **3f'** was obtained in 75% yield as a colourless oil (Hexane: Diethylether = 20:1 is used as eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.82 (m, 2H), 7.42-7.30 (m, 2H), 4.89 (t, *J* = 4.6 Hz, 1H), 4.02-3.82 (m, 7H), 2.84 (dd, *J* = 8.2, 4.7 Hz, 2H), 2.04 (ddd, *J* = 8.3, 5.7, 4.8 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, DEPT-135) δ 167.56 (C), 142.33 (C), 133.41 (CH), 130.66 (C), 129.86 (CH), 128.79 (CH), 127.60 (CH), 104.02 (CH), 65.35 (2·CH_2), 52.40 (CH_3), 35.71 (CH_2), 30.24 (CH_2).

TOF MS EI+: Calcd. for $C_{13}H_{16}O_4$: 236.1049; Found: 236.1039.

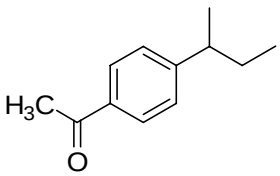
1-(4-[2-1,3-Dioxolan-2-yl)ethyl]phenyl)ethanone (**3g**)



Following general procedure for cross-coupling, **3g** was obtained in 66% yield as a colourless oil (Hexane: Acetone = 10:2 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.85 (m, 2H), 7.34-7.27 (m, 2H), 4.90 (t, *J* = 4.6 Hz, 1H), 4.03-3.84 (m, 4H), 2.82 (dd, *J* = 8.2, 4.6 Hz, 2H), 2.58 (s, 3H), 1.99 (ddd, *J* = 8.2, 5.4, 4.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 198.11 (C), 147.83 (C), 135.53 (C), 128.94 (2·CH), 128.93 (2·CH), 103.92 (CH), 65.36 (2·CH_2), 35.39 (CH_2), 30.42 (CH_2), 26.88 (CH_3).

TOF MS EI+: Calcd. for $C_{13}H_{16}O_3$: 220.1099; Found: 220.1109.

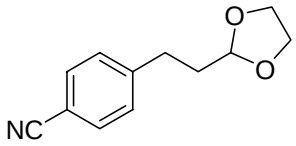
1-(4-*sec*-Butylphenyl)ethanone (**3g'**)



Following general procedure for cross-coupling, **3g'** was obtained in 84% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$)

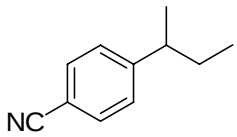
δ 7.92-7.86 (m, 2H), 7.30-7.24 (m, 2H), 2.73-2.61 (m, 1H), 2.58 (s, 3H), 1.67-1.58 (m, 2H), 1.25 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, DEPT-135) δ 198.22 (C), 153.86 (C), 135.47 (C), 128.86 (2·CH), 127.61 (2·CH), 42.12 (CH), 31.24 (CH_2), 26.85 (CH_3), 21.88 (CH_3), 12.46 (CH_3).
TOF MS EI+: Calcd. for $C_{12}H_{16}O$: 176.1201; Found: 176.1208.

4-(2-(1,3-Dioxolan-2-yl)ethyl)benzonitrile (**3h**):



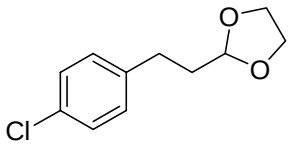
Following general procedure for cross-coupling, **3h** was obtained in 83% yield as a white solid (CH_2Cl_2 is used as a eluent): mp 64-67ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.54 (m, 2H), 7.34-7.28 (m, 2H), 4.89 (t, J = 4.5 Hz, 1H) 4.04-3.83 (m, 4H), 2.87-2.77 (m, 2H), 2.03-1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 147.4 (C), 132.3 (2·CH), 129.2 (2·CH), 119.0 (C), 109.9 (C), 103.4 (CH), 65.1 (2·CH_2), 34.8 (CH_2), 30.14 (CH_2).
Electrospray + H^+: Calcd. for $C_{12}H_{13}NO_2$: 203.0946; Found: 204.1016.

4-*sec*-Butylbenzonitrile (**3h'**)



Following general procedure for cross-coupling, **3h'** was obtained in 65% yield as a colourless oil (Hexane: EtOAc = 25:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.54 (m, 2H), 7.30-7.25 (m, 2H), 2.73-2.59 (m, 1H), 1.67-1.51 (m, 2H), 1.24 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H);
^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 153.62 (C), 132.47 (2·CH), 128.22 (2·CH), 119.47 (C), 109.97 (C), 42.22 (CH), 31.11 (CH_2), 21.70 (CH_3), 12.34 (CH_3).
TOF MS EI+: Calcd. for $C_{11}H_{13}N$: 159.1048; Found: 159.1047.
Elemental Analysis: Calcd: C, 82.97; H, 8.23; N, 8.80; Found: C, 83.21; H, 8.38; N, 8.86.

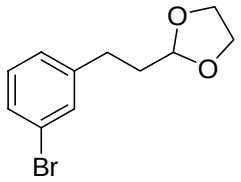
2-(4-Chlorophenethyl)-1,3-dioxolane (**3j**):



Following general procedure for cross-coupling, **3j** was obtained in 75% yield as a colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.22 (m, 2H), 7.16-7.11 (m, 2H), 7.88 (t, *J* = 4.7 Hz, 1H), 4.04-3.82 (m, 4H), 2.76-2.68 (m, 2H), 2.00-1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 140.1 (C), 131.6 (C), 129.8 (2·CH), 128.5 (2·CH), 103.6 (CH), 65.0 (2·CH_2), 35.4 (CH_2), 29.5 (CH_2).

TOF MS EI+: Calcd. for $C_{11}H_{13}ClO_2$: 212.0604; Found: 212.0613.

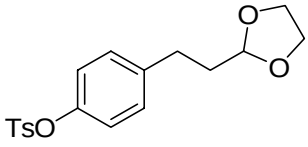
2-(3-Bromophenethyl)-1,3-dioxolane (**3k**):



Following general procedure for cross-coupling, **3k** was obtained in 75% yield as a colourless oil (Hexane: EtOAc = 100:4 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.35 (m, 1H), 7.34-7.29 (m, 1H), 7.18-7.10 (m, 2H), 4.89 (t, *J* = 4.6 Hz, 1H), 4.05-3.82 (m, 4H), 2.77-2.67 (m, 2H), 2.01-1.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 144.0 (C), 131.5 (CH), 129.94 (CH), 129.0 (CH), 127.1 (CH), 122.4 (C), 103.6 (CH), 65.0 (2·CH_2), 35.2 (CH_2), 29.7 (CH_2).

Electrospray (Na^+): Calcd. for $C_{11}H_{13}BrO_2$: 278.9991; Found: 278.9986.

4-[2-(1,3-Dioxolan-2-yl)ethyl]phenyl-4-methylbenzenesulfonate (**3l**)

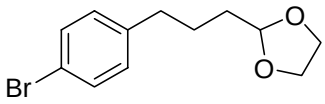


Following general procedure for cross-coupling, **3l** was obtained in 65% yield as a white solid (Hexane: EtOAc = 8:2 is used as a eluent): mp 58-61ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.67 (m, 2H), 7.33-7.27 (m, 2H), 7.13-7.08 (m, 2H), 6.91-6.85 (m, 2H), 4.86 (t, *J* = 4.6 Hz, 1H), 4.02-3.82 (m, 4H), 2.70 (dd, *J* = 8.1, 4.7 Hz, 2H), 2.45 (s,

3H), 1.93 (ddd, J = 10.4, 5.7, 4.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 148.18 (C), 145.58 (C), 141.01 (C), 132.96 (C), 130.06 (2·CH), 129.79 (2·CH), 128.87 (2·CH), 122.58 (2·CH), 103.95 (CH), 65.33 (2·CH_2), 35.65 (CH_2), 29.78 (CH_2), 22.05 (CH_3).

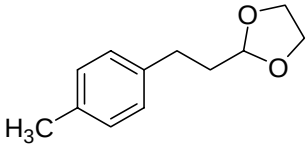
FAB mass spec.: Calcd. for $C_{18}H_{20}O_5S$: 349.1110; Found: 349.1096.

2-[3-(4-Bromophenyl)propyl]-1,3-dioxolane (**3m**)



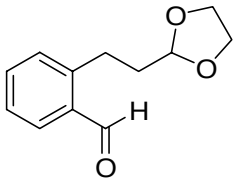
Following general procedure for cross-coupling, **3n** was obtained in 42% yield as a oil (Hexane: EtOAc = 10:1 is used as a eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 2H), 7.18-7.03 (m, 2H), 4.84 (t, J = 4.1 Hz, 1H), 3.95-3.74 (m, 4H), 2.58 (t, J = 7.1 Hz, 2H), 1.84-1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 141.41 (CH), 131.73 (2·CH), 130.59 (2·CH), 119.99 (C), 104.73 (CH), 65.28 (2·CH_2), 35.48 (CH_2), 33.67 (CH_2), 25.87 (CH_2).

2-(4-Methylphenethyl)-1,3-dioxolane (**3n**)[182]



Following general procedure for cross-coupling, **3n** was obtained in 21% yield as a oil (Hexane: EtOAc = 10:1 is used as a eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07-7.01 (m, 4H), 4.82 (t, J = 4.5 Hz, 1H), 3.95-3.85 (m, 2H), 3.81-3.77 (m, 2H); 2.67-2.62 (m, 2H), 2.25 (s, 3H); 1.93-1.87 (m, 2H).

2-[2-(1,3-Dioxolan-2-yl)ethyl]benzaldehyde (**3o**)



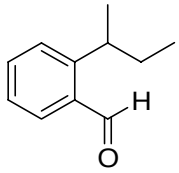
Following general procedure for cross-coupling, **3o** was obtained in 52% yield as a pale yellow oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ

[182] Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788-7789.

10.29 (br s, 1H), 7.86-7.79 (m, 1H), 7.54-7.47 (m, 1H), 7.41-7.29 (m, 2H), 4.92 (t, *J* = 4.7 Hz, 1H), 4.03-3.84 (m, 4H), 3.17 (dd, *J* = 8.1, 4.6 Hz, 2H), 1.98 (ddd, *J* = 11.4, 5.7, 4.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 192.77 (CH), 144.84 (C), 134.24 (CH), 133.21 (C), 132.32 (CH), 131.38 (CH), 127.07 (CH), 104.06 (CH), 65.37 (2·CH_2), 36.12 (CH_2), 27.22 (CH_2).

TOF MS EI+: Calcd. for $C_{12}H_{14}O_3$: 205.0865; Found: 205.0876.

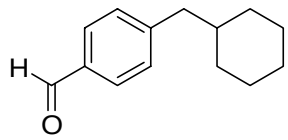
2-*sec*-Butylbenzaldehyde (**3o'**)



Following general procedure for cross-coupling, **3o'** was obtained in 70% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.38 (br s, 1H), 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.59-7.51 (m, 1H), 7.43-7.30 (m, 2H), 3.74 (sext, *J* = 6.95 Hz, 1H), 1.75-1.59 (m, 2H), 1.29 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 192.73 (CH), 150.92 (C), 134.34 (CH), 134.06 (C), 131.41 (CH), 127.12 (CH), 126.43 (CH), 34.67 (CH), 31.47 (CH_2), 22.00 (CH_3), 12.49 (CH_3).

TOF MS EI+: Calcd. for $C_{11}H_{14}O$: 162.1045; Found: 162.1045.

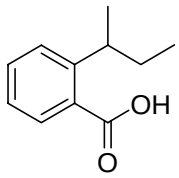
4-(Cyclohexylmethyl)benzaldehyde (**3p**)



p-Bromobenzonitrile is subjected to react under general procedure for cross-coupling, **3p** was obtained in 83% yield as a colourless oil (Hexane: EtOAc = 50:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.82-7.75 (m, 2H), 7.33-7.27 (m, 2H), 2.60-2.52 (m, 2H), 1.75-1.51 (m, 6H), 1.28-1.08 (m, 3H), 1.03-0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 192.36 (CH), 149.38 (C), 134.80 (C), 130.18 (2·CH), 130.05 (2·CH), 44.66 (CH_2), 40.01 (CH), 33.48 (2·CH_2), 26.79 (CH_2), 26.59 (2·CH_2).

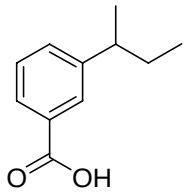
TOF MS EI+: Calcd. for $C_{14}H_{18}O$: 202.1358; Found: 202.1350.

2-*sec*-Butylbenzoic acid [**3q-*o*** (*ortho*)]



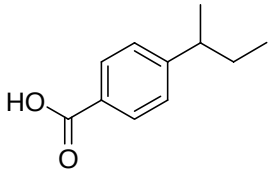
Following general procedure for cross-coupling, **3q-*o*** was obtained in 89% yield as a white solid (Hexane: EtOAc = 100:5 is used as a eluent): mp 25-27 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.84 (bs, 1H), 7.94 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56-7.47 (m, 1H), 7.41 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.30-7.20 (m, 1H), 3.80-3.64 (m, 1H), 1.79-1.53 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) *δ* 174.2 (C), 149.9 (C), 132.6 (CH), 130.8 (CH), 129.1 (C), 126.9 (CH), 125.5 (CH), 36.1 (CH), 31.1 (CH_2), 21.8 (CH_3), 12.2 (CH_3).
TOF MS EI+: Calcd. for $C_{11}H_{14}O_2$: 178.0994; Found: 178.1000.
Elemental Analysis: Calcd: C, 74.13; H, 7.92; Found: C, 74.43; H, 8.01.

3-*sec*-Butylbenzoic acid [**3q-*m*** (*meta*)]



Following general procedure for cross-coupling, **3q-*m*** was obtained in 50% yield as a white solid (Hexane: EtOAc = 100:5 is used as a eluent): mp 115-117ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (br s, 1H), 7.91-7.84 (m, 2H), 7.40-7.28 (m, 2H), 2.69-2.53 (m, 1H), 1.56 (quint, J = 7.0 Hz, 2H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) *δ* 172.4 (C), 148.2 (C), 132.7 (CH), 129.3 (C), 128.8 (CH), 128.4 (CH), 127.8 (CH), 41.5 (CH), 31.0 (CH_2), 21.7 (CH_3), 12.1 (CH_3).
TOF MS EI+: Calcd. for $C_{11}H_{14}O_2$: 178.0994; Found: 178.1002.

4-*sec*-Butylbenzoic acid [**3q-*p*** (*para*)]

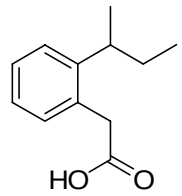


Following general procedure for cross-coupling, **3q-*p*** was obtained in 56% yield as a white solid (Hexane: EtOAc = 100:5 is used as a eluent): mp 92-94 ºC; ^{1}H NMR (300

MHz, $CDCl_3$) δ 10.63 (br s, 1H), 8.07-8.00 (m, 2H), 7.31-7.26 (m, 2H), 2.72-2.62 (m, 1H), 1.63 (quint, J = 7.3 Hz, 2H), 1.26 (d, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 170.8 (C), 154.2 (C), 130.3 (2·CH), 127.3 (2·CH), 126.8 (C), 41.9 (CH), 30.9 (CH_2), 21.5 (CH_3), 12.1 (CH_3).

TOF MS EI+: Calcd. for $C_{11}H_{14}O_2$: 178.0994; Found: 178.0999.

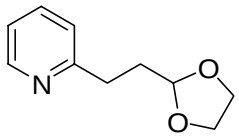
2-(2-*sec*-Butylphenyl)acetic acid (**3r**)



Following general procedure for cross-coupling, **3r** was obtained in 77% yield as a white solid and the product is purified by using DCM: DEE = 40:1: mp 40-42ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.31-7.11 (m, 4H), 3.71 (dd, *J*= 16.1 Hz, 2H), 2.91-2.75 (m, 1H), 1.72-1.51 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 178.32 (C), 146.81 (C), 131.49 (C), 131.07 (CH), 128.39 (CH), 126.43 (CH), 126.19 (CH), 38.91 (CH_2), 36.80 (CH), 31.24 (CH_2), 22.07 (CH_3), 12.58 (CH_3).

TOF MS EI+: Calcd. for $C_{12}H_{16}O_2$: 192.1150; Found: 192.1156.

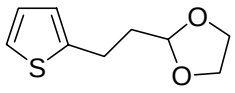
2-(2-(1,3-Dioxolan-2-yl)ethyl)pyridine (**5a**)



Following general procedure for cross-coupling, **5a** was obtained in 64% yield as a pale yellow oil (Hexane: EtOAc = 1:1 is used as a eluent): ^1H NMR (300 MHz, $CDCl_3$) δ 8.55-8.50 (m, 1H), 7.58 (td, *J* = 1.85 Hz, 1H), 7.19-7.14 (m, 1H), 7.12-7.06 (m, 1H), 4.95 (t, *J* = 4.7 Hz, 1H), 4.02-3.83 (m, 4H), 2.93 (dd, *J* = 8.1, 4.2 Hz, 2H), 2.11 (ddd, *J* = 10.2, 5.5, 4.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 161.63 (C), 149.57 (CH), 136.64 (CH), 123.10 (CH), 121.38 (CH), 104.19 (CH), 65.27 (2·CH_2), 33.96 (CH_2), 32.86 (CH_2).

TOF MS EI+ Calcd. for $C_{10}H_{13}NO_2$ (M^+-1): 178.0868; Found: 178.0874.

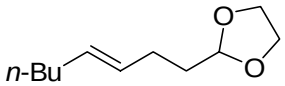
2-(2-(Thiophen-2-yl)ethyl)-1,3-dioxolane (**5b**)



Following general procedure for cross-coupling, **5b** was obtained in 65% yield as a colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.09 (m, 1H), 6.94-6.88 (m, 1H), 6.84-6.79 (m, 1H), 4.93 (t, *J* = 4.9 Hz, 1H), 4.04-3.83 (m, 4H), 3.03-2.91 (m, 2H), 2.11-1.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 161.63 (C), 149.57 (CH), 136.64 (CH), 123.10 (CH), 121.38 (CH), 104.19 (CH), 65.27 (2·CH_2), 33.96 (CH_2), 32.86 (CH_2).

TOF MS EI+: Calcd. for $C_9H_{12}O_2S$: 184.0558; Found: 184.0557.

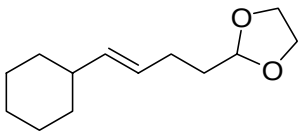
(*E*)-2-(Oct-3-enyl)-1,3-dioxolane (**7a**)



Following general procedure for cross-coupling, **7a** was obtained in 61% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51-5.35 (m, 2H), 4.86 (t, *J* = 4.8 Hz, 1H), 3.99-3.81 (m, 4H), 2.17-2.07 (m, 2H), 2.01-1.93 (m, 2H), 1.75-1.67 (m, 2H), 1.38-1.24 (m, 4H), 0.88 (t, *J* = 7.04 Hz, 3H);
^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 131.43 (CH), 129.39 (CH), 104.58 (CH), 65.25 (2·CH_2), 34.28 (CH_2), 32.60 (CH_2), 32.09 (CH_2), 27.51 (CH_2), 22.55 (CH_2), 14.32 (CH_3).

TOF MS EI+ Calcd. for $C_{11}H_{20}O_2$ (M^+-1): 183.1385; Found: 183.1391.

(*E*)-2-(4-Cyclohexylbut-3-enyl)-1,3-dioxolane (**7b**)

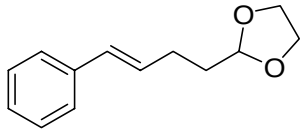


Following general procedure for cross-coupling, **7b** was obtained in 77% yield as a colourless oil (Hexane is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41-5.35 (m, 2H), 4.86 (t, *J* = 4.8 Hz, 1H), 3.99-3.81 (m, 4H), 2.15-2.06 (m, 2H), 1.95-1.82 (m, 1H), 1.75-1.62 (m, 6H), 1.34-0.95 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 137.40

(CH), 126.80 (CH), 104.57 (CH), 65.23 (2·CH_2), 41.01 (CH), 34.31 (CH_2), 33.55 (2·CH_2), 27.54 (CH_2), 26.61 (CH_2), 26.47 (2·CH_2).

TOF MS EI+: Calcd. for $C_{13}H_{22}O_2$: 210.1620; Found: 210.1631.

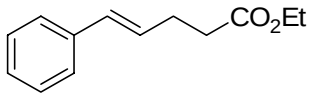
(*E*)-2-(4-Phenylbut-3-enyl)-1,3-dioxolane (**7c**)



Following general procedure for cross-coupling, **7c** was obtained in 71% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 4H), 7.22-7.15 (m, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.93 (t, *J* = 4.7 Hz, 1H), 4.02-3.83 (m, 4H), 2.41-2.31 (m, 2H), 1.89-1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 138.02 (C), 130.59 (CH), 130.13 (CH), 128.81 (2·CH), 127.26 (CH), 126.31 (2·CH), 104.33 (CH), 65.26 (2·CH_2), 33.88 (CH_2), 27.84 (CH_2).

TOF MS EI+: Calcd. for $C_{13}H_{16}O_2$: 204.1150; Found: 204.1143.

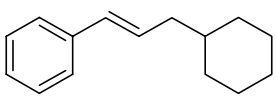
(*E*)-Ethyl 5-phenylpent-4-enolate (**7d**)



Following general procedure **A** for cross-coupling, **7d** was obtained in 51% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (m, 5H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.9, 6.5 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.59-2.43 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 173.36 (C), 138.80 (C), 131.33 (CH), 128.88 (3·CH), 127.51 (CH), 126.44 (2·CH), 60.77 (CH_2), 34.47 (CH_2), 28.69 (CH_2), 14.65 (CH_3).

TOF MS EI+: Calcd. for $C_{13}H_{16}O_2$: 204.1150; Found: 204.1161.

(*E*)-(3-Cyclohexylprop-1-enyl)benzene (**7e**)

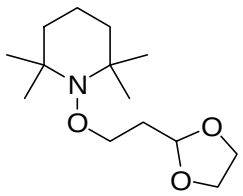


Following general procedure for cross-coupling, **7e** was obtained in 87% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.06 (m, 5H), 6.27 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.8, 7.1 Hz, 1H), 2.06-

1.98 (m, 2H), 1.73-1.53 (m, 5H), 1.40-1.24 (m, 1H), 1.24-1.03 (m, 3H), 0.95-0.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 138.35 (C), 131.08 (CH), 130.16 (CH), 128.84 (2·CH), 127.12 (CH), 126.30 (2·CH), 41.44 (CH_2), 38.60 (CH), 33.60 (2·CH_2), 26.96 (CH_2), 26.75 (2·CH_2).

TOF MS EI+: Calcd. for $C_{15}H_{20}$: 200.1565; Found: 200.1574.

1-[2-(1,3-dioxolan-2-yl)ethoxy]-2,2,6,6-tetramethylpiperidine (**10**)



Following general procedure **A** for cross-coupling, **10** was obtained in 51% yield as yellow oil (Hexane: EtOAc = 20: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (t, *J* = 4.9 Hz, 1H), 4.10-3.90 (m, 6H), 1.97 (q, *J*=6.4 Hz, 2H), 1.61-1.31 (m, 6H), 1.24 (s, 6H), 1.16 (s, 6H).

ESI MS: Calcd. for $C_{14}H_{28}NO_3$ (M^++1): 258.2063; Found: 258.2060.

III. Ni-catalyzed cross coupling of C(sp^3) electrophiles with alkylzinc and alkylmagnesium halides

IIIa. Materials, methods and optimization of the reaction conditions

The following reagents were purchased: 1-chloro-3-phenylpropane (Aldrich), benzyl chloride (Aldrich), 3-methoxybenzyl bromide (Aldrich), 2-phenylaethylbromid (EGA-chemie), 6-chloro-2-hexanone (Aldrich), 6-bromovaleronitrile (Fluka), allylamine (Aldrich), 1-bromo-3-chloropropane (Aldrich), *p*-toluenesylfonyl chloride (Merck), 4-pentyn-1-ol (Across), citronellol (Aldrich), 5-hexyn-1-ol (Aldrich), cyclohexyl iodide (Aldrich), cyclopropylmethanol (Fluka), benzyl alcohol (Merck), acetaldehyde (Aldrich).

A. General optimized procedure for the cross-coupling reactions of alkyl halides with alkylzinc bromides:

A 25 mL flask was charged with $Ni(py)_4Cl_2$ (18.11 mg, 0.040 mmol), (*S*)-(*s*-Bu)-Pybox (13.4 mg, 0.040 mmol) and a stir bar in air. The flask was sealed with a septum and backfilled with Ar. A solution of the alkyl iodide (0.406 mmol) in dry THF (2 mL) was added via syringe. After stirring for 3-4 min at rt, the resulting deep-blue solution was treated in turn with the corresponding alkylzinc bromide, (0.5 M THF solution, 0.815 mmol), and the reaction mixture was stirred at room temperature for half of the total indicated reaction time. Then again alkylzinc bromide, (0.5 M THF solution, 0.815 mmol) was added, and the reaction mixture was then stirred for the rest of the total time. The reaction mixture was then transferred to a reparatory funnel with diethyl ether (20 mL), the product was extracted with ether (2×30 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and concentrated and the residue was purified by silica gel column chromatography (Hexane: EtOAc) which afforded the final products.

B. General optimized procedure for the cross-coupling reactions of alkyl halides with alkylmagnesium reagents:

A 25 mL flask was charged with $NiCl_2$ (2.6 mg, 0.02 mmol), TMEDA (6 µl, 0.04 mmol) and a stir bar in air. The flask was sealed with a septum and backfilled with Ar. A solution of the alkyl iodide (0.406 mmol) in dry THF (2 mL) was added via syringe. After stirring for 3-4 min at rt, the resulting solution was treated in turn with the corresponding alkylmagnesium reagent, (0.37 ml (2 M in THF), 0.731 mmol), and the reaction mixture was stirred at room temperature for the indicated reaction time. The reaction mixture was then transferred to a reparatory funnel containing aqueous NH_4Cl with diethyl ether (20 mL), the phases were seperated and aqueous layer was washed with ether (2×25 mL) and the combined organic extracts were washed with brine (20 mL). After drying (over anhydrous Na_2SO_4), the solution was filtered and concentrated and the residue was purified by silica gel column chromatography (Hexane: EtOAc) which afforded the pure final products.

General procedure for iodination of alcohols

A solution of PPh_3 (1.2 mmol), imidazole (1.2 mmol) and alcohol (1 mmol) in CH_2Cl_2 (10 mL) was stirred at 5 ^oC for 5 min. To this solution resublimed iodine was added portionwise under argon atmosphere and the mixture was further stirred for the specified time. Then, it was diluted with CH_2Cl_2 (10 mL) and successively washed with aq 5% NaHCO3 and brine, dried over anhydrous Na_2SO_4 and evaporated to give a crude. Which, after flash chromatography (hexane:EtOAc), afforded the corresponding iodide.

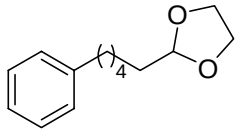
General procedure for iodination of alkyl chlorides and bromides

An alkyl halide (chloride or bromide) (1 mmol) and NaI (2 mmol) was weighed and charged to a flask fitted with a reflux condenser. The contents were flushed with argon; acetone was added (8 ml) and stirred at reflux temperature for the specified time. After completion, acetone was removed under reduced pressure and the crude was taken in a seperatory funned with diethyl ether (15 ml), and successively washed with aq 5% NH_4Cl and brine, dried over anhydrous Na_2SO_4 and evaporated to give crude. which, after flash chromatography (hexane: EtOAc), afforded the corresponding iodide.

IIIb. Experimental data

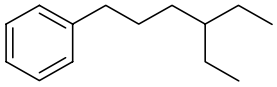
2-(5-Phenylpentyl)-1,3-dioxolane (12a)[183]

1-iodo-3-phenylpropane (**11a**)[184] was prepared from 1-chloro-3-phenylpropane by following the general iodination procedure.



Following general procedure **A** for cross-coupling, **12a** was obtained in 69% yield as a Colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 5H), 4.84 (t, *J* = 4.8 Hz, 1H), 4.00-3.81 (m, 4H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.70-1.58 (m, 4H), 1.52-1.33 (m, 4H).

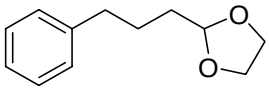
(4-Ethylhexyl)benzene (12a')



Following general procedure **A** for cross-coupling, **12a'** was obtained in 61% yield as a pale yellow oil (only hexane is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.13 (m, 5H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.66-1.50 (m, 2H), 1.34-1.17 (m, 7H), 0.82 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.37 (C), 128.75 (2·CH), 128.60 (2·CH), 125.94 (CH), 40.66 (CH), 36.82 (CH_2), 32.86 (CH_2), 29.13 (CH_2), 25.79 (2·CH_2), 11.29 (2·CH_3).

TOF MS EI+: Calcd. for $C_{14}H_{22}$: 190.1722; Found: 190.1717.

2-(3-Phenylpropyl)-1,3-dioxolane (12b)



Following general procedure **A** for cross-coupling, **12b** was obtained in 71% yield as a colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H), 7.27-7.20 (m, 3H), 4.93 (t, *J* = 4.4 Hz, 1H), 4.06-3.86 (m, 4H),

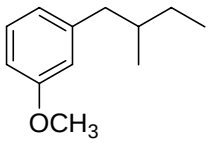
[183] Hadei, N.; Kantchev, E. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805-3807.

[184] Gallos, J.; Varvoglis, A. *J. Chem. Soc., Perkin Trans.* **1983**, *1*, 1999-2002.

2.72 (t, J = 7.3 Hz, 2H), 1.89-1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 142.48 (C), 128.75 (2·CH), 128.60 (2·CH), 126.06 (CH), 104.77 (CH), 65.17 (2·CH_2), 36.03 (CH_2), 33.75 (CH_2), 26.03 (CH_2).

TOF MS EI+: Calcd. for $C_{12}H_{16}O_2$: 191.1080; Found: 191.1072.

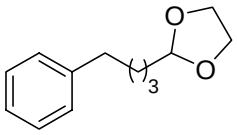
1-Methoxy-3-(2-methylbutyl)benzene (**12c**)



Following general procedure **A** for cross-coupling, **12c** was obtained in 63% yield as colourless oil (Product is purified by preparative TLC technique, hexane is used as a solvent system): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.15 (m, 1H), 6.79-6.67 (m, 3H), 3.80 (s, 3H), 2.62 (dd, J = 6.2 Hz, 1H), 2.34 (dd, J = 8.1 Hz, 1H), 1.72-1.58 (m, 1H), 1.45-1.31 (m, 1H), 1.24-1.10 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 159.85 (C), 143.79 (C), 129.35 (CH), 122.07 (CH), 115.37 (CH), 111.15 (CH), 55.49 (CH_3), 43.79 (CH_2), 36.97 (CH), 29.61 (CH_2), 19.36 (CH_3), 11.86 (CH_3).

TOF MS EI+: Calcd. for $C_{12}H_{18}O$: 178.1358; Found: 178.1365.

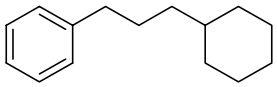
2-(4-Phenylbutyl)-1,3-dioxolane (**12d**)



Following general procedure **A** for cross-coupling, **12d** was obtained in 73% yield as a pale yellow oil (Hexane: EtOAc = 20:1 is used as a eluent) only hexane is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 7.20-7.13 (m, 3H), 4.85 (t, J = 4.7 Hz, 1H), 3.99-3.80 (m, 4H), 2.62 (t, J = 7.6 Hz, 2H), 1.74-1.60 (m, 4H), 1.54-1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 142.89 (C), 128.76 (2·CH), 128.63 (2·CH), 126.02 (CH), 104.93 (CH), 65.21 (2·CH_2), 36.27 (CH_2), 34.15 (CH_2), 31.82 (CH_2), 24.20 (CH_2).

TOF MS EI+(-1H): Calcd. for $C_{13}H_{18}O_2$: 205.1229; Found: 205.1236.

(3-Cyclohexylpropyl)benzene (**12d'**)

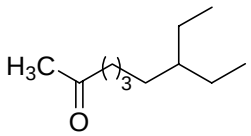


Following general procedure **A** for cross-coupling, **12d'** was obtained in 62% yield as a colourless oil (only hexane is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.30 (m, 2H), 7.28-7.20 (m, 3H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.83-1.62 (m, 7H), 1.39-1.18 (m, 6H), 1.04-0.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.38 (C), 128.77 (2·CH), 128.59 (2·CH), 125.92 (CH), 37.99 (CH), 37.57 (CH_2), 36.69 (CH_2), 33.79 (2·CH_2), 29.20 (CH_2), 27.13 (CH_2), 27.83 (2·CH_2).

TOF MS EI+: Calcd. for $C_{15}H_{22}$: 202.1722; Found: 202.1717.

7-Ethylnonan-2-one (**12e**)

6-iodo-2-hexanone (**11e**)[185] was prepared by following the general procedure of iodination reaction starting from 6-chloro-2-hexanone.

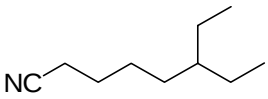


Following general procedure **A** for cross-coupling, **12e** was obtained in 66% yield as colourless oil (Hexane: EtOAc = 50:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.63-1.48 (m, 2H), 1.34-1.19 (m, 8H), 0.95-0.82 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 209.73 (C), 44.25 (CH_2), 40.59 (CH), 32.90 (CH_2), 30.22 (CH_3), 26.75 (CH_2), 25.76 (2·CH_2), 24.71 (CH_2), 11.25 (2·CH_3).

TOF MS EI+: Calcd. for $C_{11}H_{22}O$: 170.1671; Found: 170.1671.

5-Iodopentanenitrile (**12f**)

5-iodopentanenitrile (**11e**)[186] was prepared by following the general procedure of iodination reaction starting from 6-bromovaleronitrile.



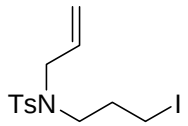
[185] Chiarello, J.; Joullie, M. M.; *Tetrahedron*, **1988**, *44*, 41-48.

[186] Chen, F.; Yuan, J.; Dai, H.; Kuang, Y.; Chu, Y. *Synthesis*, **2003**, 2155-2160.

Following general procedure **A** for cross-coupling, **12f** was obtained in 71% yield as colourless oil (Hexane: EtOAc = 50:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, *J* = 7.1 Hz, 2H), 1.71-1.57 (m, 2H), 1.49-1.17 (m, 7H), 0.93-0.83 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 120.16 (C), 40.51 (CH), 32.26 (CH_2), 26.29 (CH_2), 26.17 (CH_2), 25.67 (2·CH_2), 17.49 (CH_2), 11.18 (2·CH_3).

TOF MS EI+: Calcd. for $C_{10}H_{19}N$ (M^+-1): 152.1439; Found: 152.1432.

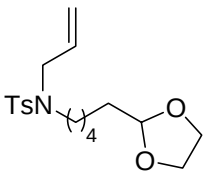
_N_-Allyl-_N_-(3-iodopropyl)-4-methylbenzenesulfonamide (**11g**)



KOH (1 mmol) was added to a solution of allyltosylamide (1 mmol), 1-bromo-3-chloropropane (1.05 mmol) and TBAB (0.1 mmol) in THF (10 ml). Allowed to stir at rt for overnight. Solvent was evaporated under reduced pressure, followed by extraction with ether. Organic layer was washed with brine, dried over Na_2SO_4 and concentrated and the crude was purified by flash chromatography (Hexane: EtOAc = 10:1 is used as a eluent) to give a chloro derivative of **11g**. Reaction with NaI (overnight), following the general procedure gave **11g**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.60 (m, 2H), 7.32-7.26 (m, 2H), 5.63 (ddt, *J* = 16.5, 10.0, 6.3 Hz, 1H), 5.20-5.08 (m, 2H), 2.81-2.77 (m, 2H), 3.21-3.15 (m, 4H), 2.42 (s, 3H), 2.19-1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.79 (C), 136.97 (C), 133.31 (CH), 130.14 (2·CH), 127.59 (2·CH), 119.74 (CH_2), 51.89 (CH_2), 48.44 (CH_2), 32.86 (CH_2), 21.88 (CH_3), 2.73 (CH_2).

_N_-(5-(1,3-Dioxolan-2-yl)pentyl)-_N_-allyl-4-methylbenzenesulfonamide (**12g**)



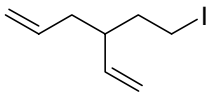
Following general procedure **A** for cross-coupling, **12g** was obtained in 63% yield as colourless oil (Hexane: EtOAc = 12:3 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.70-7.60 (m, 2H), 7.32-7.26 (m, 2H), 5.63 (ddt, *J* = 16.5, 10.0, 6.3 Hz, 1H), 5.20-5.08 (m, 2H), 4.82 (t, *J* = 4.7 Hz, 1H), 3.98-3.75 (m, 6H), 3.14-3.06 (m, 2H), 2.42 (s, 3H), 1.65-1.57 (m, 2H), 1.53-1.47 (m, 2H), 1.41-1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.42 (C), 137.60 (C), 133.71 (CH), 129.97 (2·CH), 127.48 (2·CH), 118.92 (CH_2), 104.79 (CH), 65.17 (2·CH_2), 50.85 (CH_2), 47.56 (CH_2), 34.06 (CH_2), 28.41 (CH_2), 26.90 (CH_2), 23.96 (CH_2), 21.82 (CH_3).

TOF MS EI+: Calcd. for $C_{18}H_{27}NO_4S$: 353.1661; Found: 353.1655.

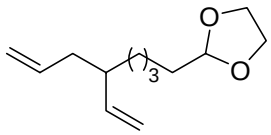
3-(2-Iodoethyl)hexa-1,5-diene (**11h**)

11h was prepared by following general procedure starting from corresponding alcohol (3-vinylhex-5-en-1-ol),[187] (2h, 77% yield).



^{1}H NMR (300MHz, $CDCl_3$) δ 5.82-5.66 (m, 1H), 5.83-5.44 (m, 1H), 5.13-4.98 (m, 4H), 3.30-3.19 (m, 1H), 3.12-3.01 (m, 1H), 2.29-2.17 (m, 1H), 2.16-2.08 (m, 1H), 2.03-1.90 (m, 1H), 1.80-1.66 (m, 1H); ^{13}C NMR (300MHz, $CDCl_3$, DEPT-135) δ 140.74 (CH), 136.46 (CH), 116.79 (CH_2), 116.42 (CH_2), 44.75 (CH), 39.40 (CH_2), 37.96 (CH_2), 5.29 (CH_2).

2-(5-Vinyloct-7-enyl)-1,3-dioxolane (**12h**)



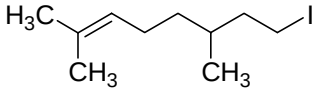
Following general procedure **A** for cross-coupling, **12h** was obtained in 66% yield as colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85-5.67 (m, 1H), 5.63-5.50 (m, 1H), 5.03-4.86 (m, 4H), 4.83 (t, *J* = 4.8 Hz, 1H), 3.99-3.80 (m, 4H), 2.14-1.99 (m, 2H), 1.90-1.71 (m, 1H), 1.69-1.59 (m, 2H), 1.50-1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.04 (CH), 137.45 (CH), 115.98 (CH_2), 114.57 (CH_2), 105.09 (CH), 65.24 (2·CH_2), 43.93 (CH), 39.85 (CH_2), 34.48 (CH_2), 34.29 (CH_2), 27.36 (CH_2), 24.51 (CH_2).

TOF MS EI+: Calcd. for $C_{13}H_{23}O_2$: 209.1542; Found: 209.1548.

[187] Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053-8060.

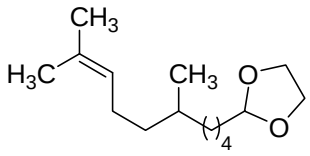
8-Iodo-2,6-dimethyloct-2-ene (**11i**)[188]

11i was prepared by following the general procedure from corresponding alcohol (citronellol).



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (*t*, *J* = 7.1 Hz, 1H), 3.29-3.11 (*m*, 2H), 2.05-1.78 (*m*, 3H), 1.72-1.511 (*m*, 1H), 1.68 (*s*, 3H), 1.60 (*s*, 3H), 1.41-1.09 (*m*, 3H), 0.88 (*d*, *J* = 6.6 Hz, 3H).

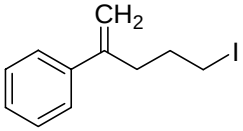
2-(5,9-Dimethyldec-8-enyl)-1,3-dioxolane (**12i**)



Following general procedure **A** for cross-coupling, **12i** was obtained in 76% yield as colourless oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13-5.05 (m, 1H), 4.84 (t, *J* = 4.9 Hz, 1H), 3.99-3.81 (m, 4H), 2.06-1.84 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.71 (m, 3H), 1.47-1.03 (m, 8H), 0.85 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 131.29 (C), 125.40 (CH), 105.06 (CH), 65.18 (2·CH_2), 37.48 (CH_2), 37.20 (CH_2), 34.32 (CH_2), 32.66 (CH), 27.31 (CH_2), 26.06 (CH_2), 25.92 (CH_3), 24.77 (CH_2), 19.92 (CH_3), 17.97 (CH_3).

EI+: Calcd. for $C_{15}H_{28}O_2$: 240.2089; Found: 240.2088.

(5-Iodopent-1-en-2-yl)benzene (**11j**)



4-phenylpent-4-en-1-ol was prepared by the reaction of pent-4-yn-1-ol and phenyl boronic acid under Pd-catalysis (79% yield).[189] The isolated alcohol was transformed to corresponding iodide (**11j**) by following the general procedure (Hexane: EtOAc = 20:1 is used as a eluent) (73% yield).

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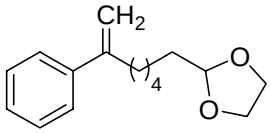
[188] Lange, G. L.; Gottardo, C. *J. Synth. Commun.* **1990**, *20*, 1473-1479.

[189] Chang H. O.; Hyung, H. J.; Ki, S. K.; Nakjoong, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 805-808.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.26 (m, 5H), 5.34-5.29 (m, 1H), 5.15-5.07 (m, 1H), 3.18 (t, *J* = 6.78 Hz, 2H), 2.64 (t, *J* = 7.30 Hz, 2H), 2.08-1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 146.83 (C), 140.87 (C), 128.75 (2·CH), 127.35 (CH), 126.82 (2·CH), 113.86 (CH_2), 36.15 (CH_2), 31.93 (CH_2), 6.93 (CH_2).

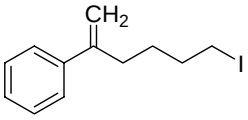
2-(6-Phenylhept-6-enyl)-1,3-dioxolane (**12j**)



Following general procedure **A** for cross-coupling, **12j** was obtained in 82% yield as colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.30 (m, 5H), 5.30-5.26 (m, 1H), 5.09-5.06 (m, 1H), 4.91-4.83 (m, 1H), 4.03-3.84 (m, 4H), 2.58-2.48 (m, 2H), 1.76-1.57 (m, 4H), 1.54-1.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 148.93 (C), 141.71 (C), 128.57 (2·CH), 127.59 (CH), 126.44 (2·CH), 112.43 (CH_2), 104.95 (CH), 65.16 (2·CH_2), 35.56 (CH_2), 34.19 (CH_2), 29.56 (CH_2), 28.48 (CH_2), 24.21 (CH_2).

EI+: Calcd. for $C_{16}H_{22}O_2$: 246.1620; Found: 246.1608.

(6-Iodohex-1-en-2-yl)benzene (**11k**)

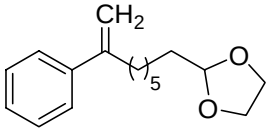


Simillar procedure is followed for the preparation of 4-phenylpent-4-en-1-ol by the use of hex-5-yn-1-ol. Followed by tosylation of alcohol by using tosyl chloride and pyridine in DCM at 0 ^{o}C. The tosylate derivative is isolated and subjected to react with NaI to afford an iodo compound (**11k**) (97% yield).[190]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 5.34-5.29 (m, 1H), 5.15-5.07 (m, 1H), 3.18 (t, *J* = 6.78 Hz, 2H), 2.57 (t, *J* = 7.30 Hz, 2H), 1.42-1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 148.26 (C), 141.39 (C), 128.70 (2·CH), 127.81 (CH), 126.50 (2·CH), 113.07 (CH_2), 34.58 (CH_2), 33.45 (CH_2), 29.38 (CH_2), 6.96 (CH_2).

[190] Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis*, **1988**, 862-867.

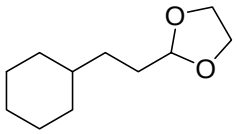
2-(7-Phenyloct-7-enyl)-1,3-dioxolane (**12k**)



Following general procedure A for cross-coupling, **12k** was obtained in 69% yield as colourless oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.21 (m, 5H), 5.25 (d, *J* = 1.5 Hz, 1H), 5.04 (q, *J* = 1.39 Hz, 1H), 4.82 (t, *J* = 4.81 Hz, 1H), 4.01-3.80 (m, 4H), 2.52-2.44 (m, 2H), 1.70-1.58 (m, 2H), 1.49-1.26 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 149.11 (C), 141.87 (C), 128.52 (2·CH), 127.60 (CH), 126.50 (2·CH), 112.43 (CH_2), 105.07 (CH), 65.21 (2·CH_2), 35.71 (CH_2), 34.27 (CH_2), 29.73 (CH_2), 29.59 (CH_2), 28.51 (CH_2), 24.41 (CH_2).

EI+: Calcd. for $C_{17}H_{24}O_2$: 260.1776; Found: 260.1774.

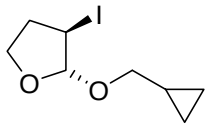
2-(2-Cyclohexylethyl)-1,3-dioxolane (**14a**)



Following general procedure **A** for cross-coupling, **17a** was obtained in 74% yield as colourless oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (t, *J* = 4.8 Hz, 1H), 4.02-3.86 (m, 4H), 1.76-1.57 (m, 7H), 1.34-1.07 (m, 6H), 0.95-0.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 105.30 (CH), 65.16 (2·CH_2), 37.88 (CH), 33.58 (2·CH_2), 31.90 (CH_2), 31.63 (CH_2), 26.98 (CH_2), 26.67 (2·CH_2).

TOF MS EI+: Calcd. for $C_{11}H_{19}O_2$ (M^+-1): 183.1385; Found: 183.1395.

(*2S,3R*)-2-(Cyclopropylmethoxy)-3-iodotetrahydrofuran (**13b**)

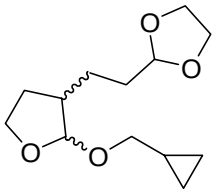


A 50 mL two necked flask equipped with a gas inlet, a septum cap, and a magnetic stirring bar was charged with cyclopropylmethanol (200 mg, 2.77 mmol, 1 equiv) dissolved in dichloromethane (3 mL). NIS (654 mg, 2.90 mmol, 1.05 equiv) was added, and the resulting suspension was cooled to 0 °C. 2,3-dihydrofuran [233 mg (251 μl),

3.32 mmol, 1.2 equiv] was added dropwise at this temperature. After 3 h of stirring, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured on ice-cooled brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried (MgSO4), and the solvents were evaporated. Purification by silica gel chromatography (hexanes/ether 20:1) afforded the alkyl iodide **13b** (744 mg, 59% yield) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (t, *J* = 4.6 Hz, 1H), 5.8 (br s, 1H), 3.98-3.81 (m, 6H), 3.42 (dd, *J* = 10.44, 7.11 Hz, 1H), 3.25 (dd, *J* = 10.44, 6.90 Hz, 1H), 2.19-2.07 (m, 2H), 1.74-1.35 (m, 5H), 1.08-0.96 (m, 1H), 0.56-0.45 (m, 2H), 0.24-0.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 108.5 (CH), 104.6 (CH), 72.4 (CH_2), 66.9 (CH_2), 65.2 (2·CH_2), 45.6 (CH), 32.6 (CH_2), 30.9 (CH_2), 27.2 (CH_2), 10.9 (CH), 3.6 (CH_2), 3.2 (CH_2).

2-(2-[(2*R,3*R**)-2-(Cyclopropylmethoxy)tetrahydrofuran-3-yl]ethyl)-1,3-dioxolane (14b_major)**



Following general procedure **A** for cross-coupling, **14b_major** was obtained in 73% yield as colourless oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (t, *J* = 4.6 Hz, 1H), 4.81 (d, *J* = 1.5 Hz, 1H), 3.98-3.81 (m, 6H), 3.42 (dd, *J* = 10.4, 7.1 Hz, 1H), 3.25 (dd, *J* = 10.4, 6.9 Hz, 1H), 2.19-2.07 (m, 2H), 1.74-1.35 (m, 5H), 1.08-0.96 (m, 1H), 0.56-0.45 (m, 2H), 0.24-0.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 108.55 (CH), 104.56 (CH), 72.43 (CH_2), 66.88 (CH_2), 65.22 (2·CH_2), 45.59 (CH), 32.65 (CH_2), 30.90 (CH_2), 27.24 (CH_2), 10.89 (CH), 3.58 (CH_2), 3.16 (CH_2).

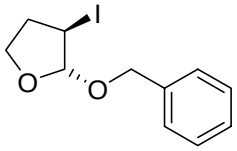
TOF MS EI+: Calcd. for $C_{13}H_{22}O_4$: 241.1440; Found: 241.1443.

2-(2-[(2*R,3*S**)-2-(Cyclopropylmethoxy)tetrahydrofuran-3-yl]ethyl)-1,3-dioxolane (14b_minor)**

Following general procedure **A** for cross-coupling, **14b_minor** was obtained in 6% yield as colourless oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, *J* = 4.9 Hz, 1H), 4.81 (t, *J* = 4.5 Hz, 1H), 3.98-3.78 (m, 6H), 3.47 (dd,

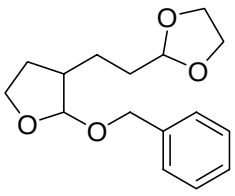
J = 10.5, 6.6 Hz, 1H), 3.24 (dd, *J* = 10.6, 6.8 Hz, 1H), 1.79-1.59 (m, 2H), 1.79-1.58 (m, 4H), 1.08-0.78 (m, 2H), 0.55-0.40 (m, 2H), 0.26-0.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 105.01 (CH), 103.39 (CH), 71.72 (CH_2), 67.00 (CH_2), 65.25 (2·CH_2), 44.37 (CH), 33.15 (CH_2), 29.71 (CH_2), 23.55 (CH_2), 10.89 (CH), 3.55 CH_2), 2.94 (CH_2).

(*2S,3R*)-2-(Benzyloxy)-3-iodotetrahydrofuran (**13c**)



13c was prepared by following the same procedure as used for the preparation of **13b**, benzyl alcohol is used instead of cyclopropylmethanol. (79% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 5.44 br s, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.24-4.02 (m, 3H), 2.67 (ddt, *J* = 8.2, 6.3 Hz, 1H), 2.27-2.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 137.88 (C), 128.77 (2·CH), 128.19 (2·CH), 128.11 (CH), 110.06 (CH), 69.27 (CH_2), 67.41 (CH_2), 35.95 (CH_2), 24.98 (CH).

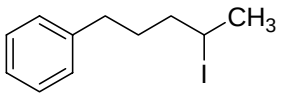
2-(2-[(2*R,3R*)-2-(Benzyloxy)tetrahydrofuran-3-yl]ethyl)-1,3-dioxolane** (**14c**)



Following general procedure **A** for cross-coupling, **14c** was obtained in 72% yield as colourless oil (Hexane: EtOAc = 8:2 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 4.88 (d, *J* = 1.4 Hz, 1H), 4.84 (t, *J* = 4.6 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.01-3.80 (m, 6H), 2.27-2.10 (m, 2H), 1.80-1.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 138.62 (C), 128.75 (2·CH), 128.62 (2·CH), 127.89 (CH), 108.21 (CH), 104.56 (CH), 69.43 (CH_2), 67.18 (CH_2), 65.27 (2·CH_2), 45.71 (CH), 32.65 (CH_2), 30.88 (CH_2), 27.18 (CH_2).

EI+: Calcd. for $C_{16}H_{21}O_4$ (M^+-1) 277.143984; Found: 277.143400.

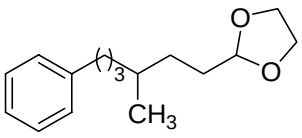
(4-Iodopentyl)benzene (**13d**)



To a double-necked flask containing Mg (53 mg, 2.2 mmol) and anhydrous Et_2O (3 mL), 1-chloro-3-phenylpropane (309 mg, 2 mmol) and catalytic amount of I_2 (10 mg were added, the resulting solution was heated at reflux temperature for 1 h. then stirred for overnight. Then, a solution of acetaldehyde (140 µL, 2.5 mmol) in anhydrous Et_2O (5 mL) was added drop wise. Then, the mixture was stirred at room temperature for a further 30 min. After filtration the mixture was added to an aqueous solution of HCl (30 mL, 1.2 M) and the organic layer separated and washed with H_2O. The aqueous phase was extracted with Et_2O and the combined organic phases dried ($MgSO_4$), filtered and evaporated at atmospheric pressure (35 °C). The crude residue was purified by flash chromatography (Hexane: EtOAc = 20:1 is used as an eluent) intermediate 5-phenylpentan-2-ol,[191] 88% yield as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.14 (m, 5H), 3.88-3.75 (m, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.82-1.55 (m, 2H), 1.54-1.34 (m, 3H), 1.18 (d, *J* = 6.18 Hz, 3H).

This alcohol (5-phenylpentan-2-ol) is subjected to general procedure for conversion to iodo compound (**13d**), (Hexane: EtOAc = 20:1 is used as an eluent, 91% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.10 (m, 5H), 4.27-4.12 (m, 1H), 2.71-2.55 (m, 2H), 1.91 (d, *J* = 6.81 Hz, 3H), 1.87-1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 142.26 (C), 128.75 (4·CH), 126.26 (CH), 42.66 (CH_2), 35.34 (CH_2), 31.85 (CH_2), 30.50 (CH), 29.29 (CH_2).

2-(3-Methyl-6-phenylhexyl)-1,3-dioxolane (**14d**)

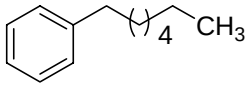


Following general procedure **A** for cross-coupling, **14d** was obtained in 69% yield as a Colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 2H), 7.21-7.12 (m, 3H), 4.82 (t, *J* = 4.8 Hz, 1H), 4.00-3.81 (m, 4H),

[191] Kropp, P. J. *J. Org. Chem.* **1995**, *60*, 4146-4152.

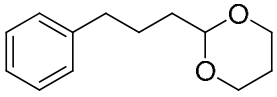
2.58 (t, J = 7.7 Hz, 2H), 1.73-1.52 (m, 4H), 1.51-1.30 (m, 3H), 1.28-1.13 (m, 2H), 0.87 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.20 (C), 128.75 (2·CH), 128.60 (2·CH), 125.95 (CH), 105.32 (CH), 65.20 (2·CH_2), 36.93 (CH_2), 36.64 (CH_2), 32.98 (CH), 31.85 (CH_2), 31.35 (CH_2), 29.30 (CH_2), 19.85 (CH_3).
TOF MS EI+: Calcd. for $C_{16}H_{24}O_2$: 248.1776; Found: 248.1765.

Heptylbenzene (**18a**)



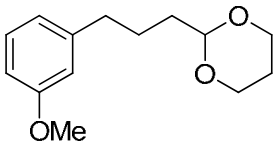
Following general procedure **B** for cross-coupling, **18a** was obtained in 75% yield as a Colourless oil (Hexane is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.14 (m, 5H), 2.61 (t, J = 7.8 Hz, 2H), 1.71-1.55 (m, 2H), 1.42-1.21 (m, 8H), 0.89 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.36 (C), 128.79 (2·CH), 128.60 (2·CH), 125.93 (CH), 36.39 (CH_2), 32.22 (CH_2), 31.92 (CH_2), 29.71 (CH_2), 29.58 (CH_2), 23.06 (CH_2), 14.48 (CH_3).
TOF MS EI+: Calcd. for $C_{13}H_{20}$: 176.1565; Found: 176.1569.

2-(3-Phenylpropyl)-1,3-dioxane (**18l**)



Following general procedure **B** for cross-coupling, **18l** was obtained in 31% yield as a colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 4.59 (t, J = 4.9 Hz, 1H), 4.23-4.10 (m, 2H), 3.90-3.69 (m, 2H), 2.70 (t, J = 7.4 Hz, 2H), 2.26-2.00 (m, 1H), 1.89-1.55 (m, 4H), 1.46-1.32 (1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 142.70 (C), 128.85 (2·CH), 128.67 (2·CH), 126.11 (CH), 102.64 (CH), 67.30 (2·CH_2), 36.15 (CH_2), 35.26 (CH_2), 26.27 (CH_2), 26.19 (CH_2).
TOF MS EI+: Calcd. for $C_{13}H_{17}O_2$: 205.1229; Found: 205.1235.

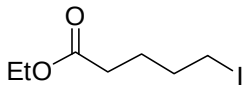
2-[3-(3-Methoxyphenyl)propyl]-1,3-dioxane (**18m**)



Following general procedure **B** for cross-coupling, **18m** was obtained in 41% yield as a colourless oil (Hexane: EtOAc = 15:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.12 (m, 1H), 6.84-6.60 (m, 3H), 4.52 (t, *J* = 4.9 Hz, 1H), 4.20-4.05 (m, 2H), 3.79 (s, 3H), 3.85-3.65 (m, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.21-1.98 (m, 1H), 1.84-1.55 (m, 4H), 1.46-1.32 (1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 160.03 (C), 144.34 (C), 129.60 (CH), 121.48 (CH), 114.57 (CH), 111.50 (CH) 102.62 (CH), 67.29 (2·CH_2), 55.51 (CH_2), 36.19 (CH_2), 35.44 (CH_2), 26.46 (CH_2), 26.08 (CH_3).
TOF MS EI+: Calcd. for $C_{14}H_{20}O_3$: 236.1412; Found: 236.1389.

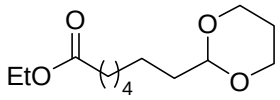
Ethyl 5-iodopentanoate (**11n**)[192]

11n was prepared by the reaction of ethyl 5-bromopentanoate with NaI by following the general procedure as described above. (Hexane: EtOAc = 20:1 is used as an eluent, 93% yield)



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.18 (t, *J* = 6.8 Hz, 2H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.93-1.63 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H).

Ethyl 7-(1,3-dioxolan-2-yl)heptanoate (**18n**)



Following general procedure **B** for cross-coupling, **18n** was obtained in 43% yield as a colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (t, *J* = 5.1 Hz, 2H), 4.21-3.99 (m, 4H), 3.71-3.59 (m, 2H), 2.25 (t, *J* = 7.6 Hz, 2H), 1.71-1.51 (m, 4H), 1.45-1.25 (m, 8H), (1.23, t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 174.19 (C), 102.74 (CH), 67.27 (2·CH_2), 60.41 (CH_2), 35.43 (CH_2), 34.72 (CH_2), 29.48 (CH_2), 29.39 (CH_2), 26.25 (CH_2), 25.25 (CH_2), 24.15 (CH_2), 14.63 (CH_3).

[192] Chow, C. P.; Shea, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 3678-3679.

IV. Ni-catalyzed cascade formation of $C(sp^3)$–$C(sp^3)$ bonds by cyclization and cross-coupling reactions of iodoalkanes with alkylzinc halides

IVa. Materials, methods and optimization of the reaction conditions

The following reagents were purchased: Allyl alcohol (Fluka), 2-methyl-2-propen-1-ol (Aldrich), 2,3-dihydrofuran (Aldrich), 3,4-dihydro-2*H*-pyran (Aldrich), cyclopentene (Aldrich), allylamine (Aldrich), *p*-toluenesulfonyl chloride (Merck), 1,2-dibromoethyane (Aldrich), dimethyl allylmalonate (Aldrich), ethyl vinyl ether (Aldrich), 5-bromo-1-pentene (Aldrich), 2-bromobenzyl alcohol (Aldrich), allyl bromide (Aldrich), 6-bromo-1-hexene (Aldrich), 2-allyloxyethanol (Aldrich), cyclopropylmethanol (Fluka), cyclohexen oxide (Aldrich), *N*-allylaniline (Aldrich).

Iodoketals were synthesized by reaction of 2, 3-dihydrofuran with the suitable allylic alcohol and NIS according to the described procedure.[193] Iodoethers were prepared in the same way from cyclopentene. Compounds, 6-iodohex-1-ene,[194] 3-(2-iodoethoxy)prop-1-ene,[195] were previously described.

A. General optimized procedure for the cross-coupling reactions of alkyl halides with alkylzinc bromides:

A 25 mL flask was charged with $Ni(py)_4Cl_2$ (18.11 mg, 0.040 mmol), (*S*)-(*s*-Bu)-Pybox (13.4 mg, 0.040 mmol) and a stir bar in air. The flask was sealed with a septum and backfilled with Ar. A solution of the alkyl iodide (0.406 mmol) in dry THF (2 mL) was added via syringe. After stirring for 3-4 min at rt, the resulting deep-blue solution was treated in turn with the corresponding alkylzinc bromide, (0.5 M THF solution, 0.815 mmol), and the reaction mixture was stirred at room temperature for half of the total indicated reaction time. Then again alkylzinc bromide, (0.5 M THF solution, 0.815 mmol) was added, and the reaction mixture was then stirred for the rest of the total time. The reaction mixture was then transferred to a reparatory funnel with diethyl ether (20 mL), the product was extracted with ether (2×30 mL) and the combined

[193] (a) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743-5753. (b) Middelton, D. S.; Simpkins, N. S. *Synth. Commun*. **1987**, *19*, 21-29.

[194] Hodgson, D. M.; Labande, A. H.; Pierard, F.; Exposito C. A. *J. Org Chem.* **2003**, *68*, 6153-6159.

[195] Hegedus, L. S.; Thompson, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 5663-5669.

organic extracts were washed with water (20 mL) and brine (20 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and concentrated and the residue was purified by silica gel column chromatography (Hexane: EtOAc) which afforded the final products.

B. General optimized procedure for the cross-coupling reactions of alkyl halides with alkylmagnesium reagents:

A 25 mL flask was charged with $NiCl_2$ (2.6 mg, 0.02 mmol), TMEDA (6 µl, 0.04 mmol) and a stir bar in air. The flask was sealed with a septum and backfilled with Ar. A solution of the alkyl iodide (0.406 mmol) in dry THF (2 mL) was added via syringe. After stirring for 3-4 min at rt, the resulting solution was treated in turn with the corresponding alkylmagnesium reagent, (0.37 ml (2 M in THF), 0.731 mmol), and the reaction mixture was stirred at room temperature for the indicated reaction time. The reaction mixture was then transferred to a reparatory funnel containing aqueous NH_4Cl with diethyl ether (20 mL), the phases were seperated and aqueous layer was washed with ether (2×25 mL) and the combined organic extracts were washed with brine (20 mL). After drying (over anhydrous Na_2SO_4), the solution was filtered and concentrated and the residue was purified by silica gel column chromatography (Hexane: EtOAc) which afforded the pure final products.

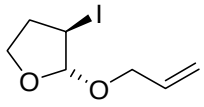
General procedure for the preparation of iodoketals

A 50 mL two necked flask equipped with a gas inlet, a septum cap, and a magnetic stirring bar was charged with allyl alcohol (0.78 ml, 13 mmol, 1 equiv) dissolved in dichloromethane (15 mL). NIS (2.71 g, 24 mmol, 1.05 equiv) was added, and the resulting suspension was cooled to 0 °C. 2,3-dihydrofuran [1.05 g (1.13 ml), 3 mmol, 1.25 equiv] was added dropwise at this temperature. After 3 h of stirring, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured on ice-cooled brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was dried (MgSO4), and the solvents were evaporated. Purification by silica gel chromatography (hexanes/ether 20:1) afforded the iodoalkane **19a**, (3.1 g, 81% yield).

IVb. Experimental data

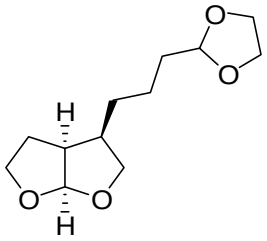
(*2S,3R*)-2-(Allyloxy)-3-iodotetrahydrofuran (**19a**)[192a]

19a was prepared by following the general procedure for preparation of iodoketals.



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94-5.81 (m, 1H), 5.38 (br s, 1H), 5.27 (dm, *J* = 17.2 Hz 1H), 5.18 (dm, *J* =10.4 Hz 1H), 4.20-3.93 (m, 5H), 2.69-2.57 (m, 1H), 2.24-2.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 134.45 (CH), 117.65 (CH_2), 110.18 (CH), 68.39 (CH_2), 67.36 (CH_2), 35.97 (CH_2), 24.95 (CH).

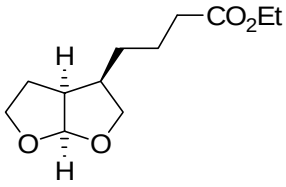
(*3R*,3aS*,6aR**)-3-[3-(1,3-Dioxolan-2-yl)propyl]hexahydrofuro [2,3-*b*]furan (**20a**)



Following general procedure **A** for cross-coupling, **20a** was obtained in 79% yield as pale yellow oil (Hexane: EtOAc = 6:4 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, *J* = 5.0 Hz, 1H), 4.84 (t, *J* = 4.7 Hz, 1H), 3.98-3.81 (m, 7H), 3.39 (dd, *J*= 11.4, 8.4 Hz, 1H), 2.83-2.72 (m, 1H), 2.35-2.21 (m, 1H), 1.89-1.76 (m, 2H), 1.70-1.61 (m, 2H), 1.49-1.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 109.91 (CH), 104.40 (CH), 72.70 (CH_2), 69.26 (CH_2), 65.05 (2·CH_2), 45.53 (CH), 42.37 (CH), 34.12 (CH_2), 27.69 (CH_2), 25.12 (CH_2), 23.10 (CH_2).

TOF MS EI+: Calcd. for $C_{12}H_{20}O_4$: 228.1362; Found: 228.1371.

Ethyl 4-[(*3R*,3aS*,6aR**)-hexahydrofuro[2,3-*b*]furan-3-yl]butanoate (**20a'**)

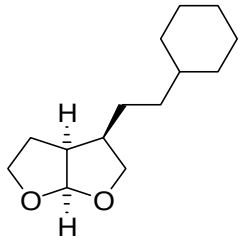


Following general procedure **A** for cross-coupling, **20a'** was obtained in 65% yield as pale yellow oil (Hexane: EtOAc = 8:2 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$)

[192a] Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743-5753

δ 5.70 (d, *J* = 5.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.95-3.81(m, 3H), 3.39 (dd, *J*=11.4, 8.5 Hz, 1H) 2.84-2.73 (m, 1H), 2.34-2.23(m, 3H), 1.88-1.79 (m, 2H), 1.72-1.53 (m, 2H), 1.46-1.35 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT-135) δ 173.59 (C), 110.05 (CH_2), 72.74 (CH_2), 69.42 (CH_2), 60.66 (CH_2), 42.31 (CH), 42.31 (CH), 34.57 (CH_2), 27.35 (CH_2), 25.19 (CH_2), 24.09 (CH_2), 14.55 (CH_3).
TOF MS EI+: Calcd. for $C_{12}H_{19}O_4$ (M^+-1): 227.1283; Found: 227.1283.

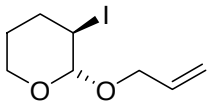
(*3R*,3aS*,6aR)-3-(2-Cyclohexyl)hexahydrofuro[2,3-*b*]furan** (**20a''**)



Following general procedure **A** for cross-coupling, **20a''** was obtained in 60% yield as colourless oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, *J* = 4.9 Hz, 1H), 3.95-3.81 (m, 3H), 3.39 (dd, *J* = 11.4, 8.4 Hz, 1H), 2.83-2.72 (m, 1H), 2.31-2.17 (m, 1H), 1.91-1.77 (m, 2H), 1.75-1.58 (m, 6H), 1.43-1.10 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ110.14 (CH), 73.12 (CH_2), 69.49 (CH_2), 45.77 (CH), 42.77 (CH), 38.23 (CH), 36.57 (CH_2), 33.78 (2·CH_2), 27.00 (2·CH_2), 26.70 (CH_2), 25.30 (CH_2), 25.15 (CH_2).
TOF MS EI+: Calcd. for $C_{14}H_{24}O_2$: 224.1776; Found: 224.1767.

(*2S,3R*)-2-(Allyloxy)-3-iodotetrahydro-2*H*-pyran (**19b**)[196]

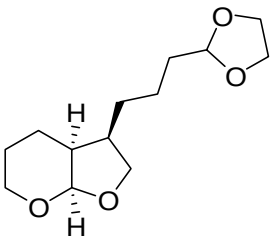
19b was prepared by following the general procedure for preparation of iodoketals.



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95-5.82 (*m*, 1H), 5.28 (*dm*, *J* =17.2 Hz, 1H), 5.16 (*dm*, *J* =10.4 Hz, 1H), 4.63 (*d*, *J* = 5.4 Hz, 1H), 4.24 (*ddm*, *J* =12.8, 5.2 Hz, 1H), 4.10-3.90 (*m*, 3H), 2.39-2.29 (*m*, 1H), 2.03-1.92 (*m*, 1H), 1.79-1.67 (*m*, 1H), 1.59-1.47 (*m*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 134.76 (CH), 117.49 (CH_2), 101.56 (CH), 68.96 (CH_2), 63.50 (CH_2), 33.36 (CH_2), 29.74 (CH_2), 25.56 (CH).

[196] Ollivier, C.; Renauld, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717-4727.

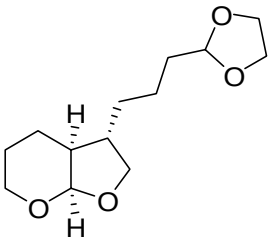
(*3R*,3aS*,7aR)-3-[3-(1,3-Dioxolan-2-yl)propyl]hexahydrofuro[2,3-*b*]pyran** [**20b** (**major**)]



Following general procedure **A** for cross-coupling, **20b** (**major**) was obtained in 76% yield as pale yellow oil (Hexane: EtOAc = 7:3 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24, (d, J = 3.8 Hz, 1H), 4.81 (t, J = 4.7 Hz, 1H), 4.01-3.57 (m, 8H), 2.82-2.25 (m, 1H), 1.97-1.86 (m, 1H), 1.71-1.51 (m, 5H), 1.49-1.23 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT-135) δ 104.59 (CH), 102.31 (CH), 70.30 (CH_2), 65.16 (2·CH_2), 61.23 (CH_2), 41.34 (CH), 36.74 (CH), 34.26 (CH_2), 27.30 (CH_2), 23.51 (CH_2), 23.00 (CH_2), 19.49 (CH_2).

EI+: Calcd. for $C_{13}H_{22}O_4$: 242.151809; Found: 242.151100.

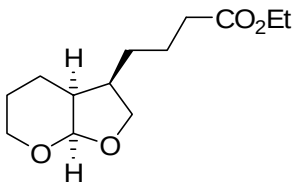
(*3R*,3aR*,7aS)-3-[3-(1,3-dioxolan-2-yl)propyl]hexahydrofuro[2,3-*b*]pyran** [**20b** (**minor**)] (7% yield, from mixture of two diastereomers).



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (d, J = 3.6 Hz, 1H), 4.26 (t, J = 8.2 Hz, 1H), 3.95-3.35 (m, 8H), 1.84-1.77 (m, 1H), 1.73-1.69 (m, 1H), 1.66-1.09 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ most signals overlap with those of the other major isomer.

Ethyl 4-[(3*R, 3a*S**,7a*R**)-hexahydro[2, 3-*b*]pyran-3-yl]butanoate** (**20b'**)

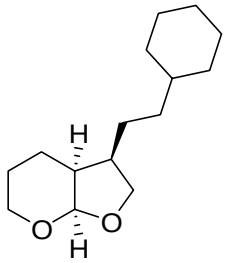


Following general procedure **A** for cross-coupling, **20b'** was obtained in 94% yield (combined yield for both diastereoisomers) as pale yellow oil (Hexane: EtOAc = 9:1 is

used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (d, *J* = 3.6 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.94 (t, *J* = 8.2 Hz 1H), 3.77- 3.58 (m, 3H), 2.33-2.25 (m, 3H), 1.99-1.88 (m, 1H), 1.65-1.32 (m, 8H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3 (C), 102.05 (CH), 69.89 (CH_2), 61.1 (CH_2), 60.3 (CH_2), 40.9 (CH), 36.26 (CH), 39.5 (CH_2), 26.6 (CH_2), 23.6 (CH_2), 23.18 (CH_2), 19.3 (CH_2), 14.16 (CH_3).

TOF MS EI+: Calcd. for $C_{13}H_{22}O_4$: 242.1568; Found: 242.1572.

(*3R*,3aS*,7aR)-3-(2-Cyclohexylethyl)hexahydrofuro[2,3-*b*]pyran** (**20b''**)

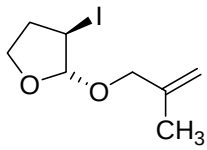


Following general procedure **A** for cross-coupling, **20b''** was obtained in 81% yield (combined yield for both diastereoisomers) as yellow oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (d, *J* = 3.6 Hz, 1H), 3.93 (t, *J* = 7.8 Hz, 1H), 3.78-3.64 (m, 1H), 3.66-3.58 (m, 2H), 2.33-2.16 (m, 1H), 1.97-1.87 (m, 1H), 1.73-1.52 (m, 8H), 1.45-1.30 (m, 2H), 1.28-1.06 (m, 7H), 0.93-0.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 102.46 (CH), 70.58 (CH_2), 61.34 (CH_2), 41.67 (CH), 38.26 (CH), 36.87 (CH), 36.38 (CH_2), 33.80 (2·CH_2), 27.03 (CH_2), 26.73 (2·CH_2), 24.64 (CH_2), 23.66 (CH_2), 19.2 (CH_2).

EI+: Calcd. for $C_{15}H_{25}O_2$ (M^+-1): 237.185455; Found: 237.185500.

(*2S,3R*)-3-Iodo-2-(2-methylallyloxy)tetrahydrofuran (**19c**)

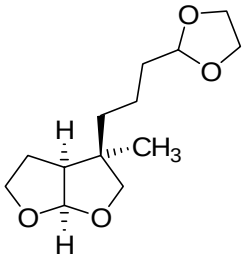
19c was prepared by following the general procedure for preparation of iodoketals.



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 4.96-4.85 (*m*, 2H), 4.31-3.58 (m, 5H), 2.70-2.50 (m, 1H), 2.25-2.12 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 141.94 (CH_2), 112.76 (CH_2), 110.09 (CH), 71.25 (CH_2), 67.35 (CH_2), 36.02 (CH_2), 24.95 (CH), 19.89 (CH_3).

TOF MS EI+: Calcd. for $C_8H_{13}O_2I$: 267.9960; Found: 267.9977.

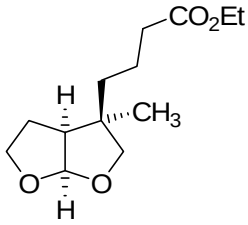
(*3R*,3aS*,6aR)-3-[3-(1,3-dioxolan-2-yl)propyl]hexahydro-3-methylfuro[2,3-*b*]furan** (**20c**)



Following general procedure **A** for cross-coupling, **20c** was obtained in 64% yield as pale yellow oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (d, *J* = 4.8 Hz, 1H), 4.84 (t, *J* = 4.7 Hz, 1H), 4.02-3.76 (m, 6H), 3.54 (dd, *J* = 12.1, 8.4 Hz, 2H), 2.42-2.33 (m, 1H), 1.90-1.32 (m, 8H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 109.97 (CH), 104.63 (CH), 78.85 (CH_2), 69.15 (CH_2), 65.23 (2·CH_2), 52.90 (CH), 45.31 (C), 34.84 (2·CH_2), 26.49 (CH_2), 25.63 (CH_3), 19.93 (CH_2).

TOF MS EI+: Calcd. for $C_{13}H_{21}O_4$ (M^+-1): 241.1450; Found: 241.1440.

Ethyl 4-[(*3R*,3aS*,6aR)-hexahydro-3-methylfuro[2,3-*b*]furan-3-yl]butanoate** (**20c'**)

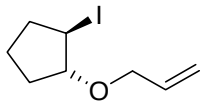


Following general procedure **A** for cross-coupling, **20c'** was obtained in 68% yield as pale yellow oil (Hexane: EtOAc = 7:3 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (d, *J* = 4.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.96-3.77 (m, 2H), 3.55 (dd, *J* = 11.2, 8.3 Hz, 1H) 2.46-2.26 (m, 3H), 1.94-1.58 (m, 4H), 1.46-1.20 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H) 1.1 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT-135) δ 173.67 (C), 109.98 (CH_2), 78.79 (CH_2), 69.16 (CH_2), 60.72 (CH_2), 52.79 (CH), 45.20 (C), 35.03 (CH_2), 34.31 (CH_2), 26.46 (CH_2), 25.58 (CH_3), 20.86 (CH_2), 14.61 (CH_3).

EI+: Calcd. for $C_{13}H_{21}O_4$ (M^+-1): 241.143984; Found: 241.143800.

(*1R,2R*)-1-(Allyloxy)-2-iodocyclopentane (**19d**)

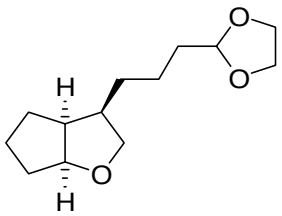
19d was prepared by following the general procedure for preparation of iodoketals, from cyclopentene, NIS and allyl alcohol.



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 15.9, 10.6, 5.5 Hz, 1H), 5.27 (dm, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dm, *J* = 10.4, 1.4 Hz, 1H), 4.31-4.18 (m, 2H), 4.08-3.92 (m, 2H), 2.41-1.98 (m, 3H), 1.95-1.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 135.07 (CH), 117.41 (CH_2), 89.39 (CH), 70.83 (CH_2), 36.95 (CH_2), 31.26 (CH), 30.41 (CH_2), 23.05 (CH_2).

EI+: Calcd. for $C_8H_{13}OI$: 252.0011; Found: 252.0008.

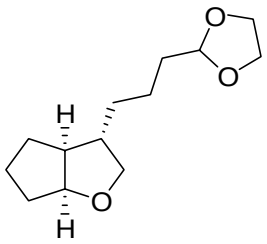
Ethyl 4-[(3*R,3a*S**,6a*S**)-3-(3-(1,3-dioxalan-2-yl)propyl)]hexahydro-2*H*-cyclopenta[*b*]furan** [**20d** (**major**)]



Following general procedure **A** for cross-coupling, **20d** (**major**) was obtained in 49% yield as pale yellow oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (t, *J* = 4.7 Hz, 1H), 4.53-4.46 (m, 1H), 3.93-3.79 (m, 5H), 3.29 (dtd, *J* = 8.4, 2.1, 1.7 Hz, 1H), 2.56-2.44 (m, 1H), 2.34-2.20 (m, 1H), 1.83-1.29 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 102.73 (CH), 86.25 (CH), 72.56 (CH_2), 65.12 (2.CH_2), 46.71 (CH), 43.50 (CH), 35.04 (CH_2), 34.38 (CH_2), 28.09 (CH_2), 26.26 (CH_2), 25.37 (CH_2), 23.61 (CH_2).

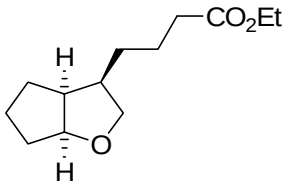
TOF MS EI+: Calcd. for $C_{13}H_{20}O_3$ (M^+-2): 226.1569; Found: 226.1576.

Ethyl 4-[(3*S,3a*S**,6a*S**)-3-(3-(1,3-dioxalan-2-yl)propyl)]hexahydro-2*H*-cyclopenta[*b*]furan** [**20d** (**minor**)]



Following general procedure **A** for cross-coupling, **20d** (**minor**) was obtained in 27% yield as pale yellow oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (t, *J* = 4.8 Hz, 1H), 4.42-4.35 (m, 1H), 4.01-3.78 (m, 5H), 3.17 (dt, *J* = 8.7 Hz, 1H) 2.24-2.12 (m, 1H), 1.84-1.31 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 104.83 (CH), 85.47 (CH), 73.98 (CH_2), 65.24 (2·CH_2), 50.10 (CH), 48.27 (CH), 34.51 (CH_2), 34.42 (CH_2), 33.26 (CH_2), 32.95 (CH_2), 24.24 (CH_2), 23.38 (CH_2).
TOF MS EI+: Calcd. for $C_{13}H_{22}O_3$: 226.1569; Found: 226.1566.

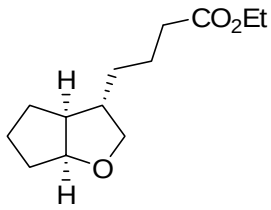
Ethyl 4-[(3*R,3a*S**,6a*S**)-hexahydro-2*H*-cyclopenta[*b*]furan-3-yl]butanoate** [**20d'** (**major**)]:



Following general procedure **A** for cross-coupling, **20d'** (**major**) was obtained in 46% yield as pale yellow oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (ddd, *J* = 5.8, 2.4 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.84(t, *J*= 7.7 Hz, 1H), 3.28 (dd, *J* = 10.6, 8.3 Hz, 1H) 2.56-2.44 (m, 1H), 2.33-2.19 (m, 3H), 1.83-1.29 (m, 10H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 173.83 (C), 86.33 (CH), 72.53 (CH_2), 60.61 (CH_2), 46.69 (CH), 43.33 (CH), 35.05 (CH_2), 34.82 (CH_2), 27.72 (CH_2), 26.31 (CH_2), 25.39 (CH_2), 24.55 (CH_2), 14.60 (CH_3).

TOF MS EI+: Calcd. for $C_{13}H_{20}O_3$ (M^+-2): 224.1412; Found: 224.1420.

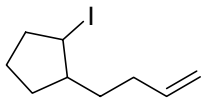
Ethyl 4-[(3*S,3a*S**,6a*S**)-hexahydro-2*H*-cyclopenta[*b*]furan-3-yl]butanoate** [**20d'** (**minor**)]:



Following general procedure **A** for cross-coupling, **20d'** (**minor**) was obtained in 35% yield as pale yellow oil (Hexane: EtOAc = 9:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (t, *J* = 6.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.93 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.17 (t, *J* = 8.6 Hz, 1H) 2.29 (t, *J* = 7.4 Hz, 2H), 2.23-2.13 (m, 1H), 1.90-1.32 (m, 11H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 173.87 (C), 85.48 (CH), 73.87 (CH_2), 60.64 (CH_2), 50.06 (CH), 48.04 (CH), 34.86 (CH_2), 34.39 (CH_2), 32.97 (CH_2), 32.81 (CH_2), 24.27 (CH_2), 24.24 (CH_2), 14.62 (CH_3).
TOF MS EI+: Calcd. for $C_{13}H_{20}O_3$ (M^+-2): 224.1412; Found: 224.1415.

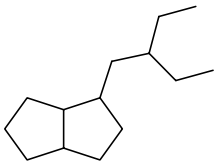
1-(But-3-enyl)-2-iodocyclopentane (**19e**)[197]

19e was prepared by following the general procedure for iodination of alcohols (see p 192), starting from 2-(but-3-enyl)cyclopentanol.[198]



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1H), 5.08-4.91 (m, 2H), 4.58-4.51 (m, 1H), 2.40-1.88 (m, 5H), 1.81-1.35 (m, 5H), 0.97-0.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 138.89 (CH), 115.08 (CH_2), 46.57 (CH), 45.59 (CH), 39.31 (CH_2), 36.35 (CH_2), 32.59 (CH_2), 29.33 (CH_2), 22.12 (CH_2).

1-(2-Ethylbutyl)octahydropentalene (**20e**)



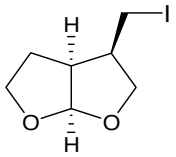
Following general procedure **A** for cross-coupling, **20e** was obtained in 73% yield as colourless oil (Hexane is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47-2.21 (m,

[197] Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2001**, *129*, 2713-2717.

[198] Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444-2451.

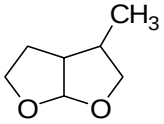
1H),1.96-1.42 (m, 6H), 1.39-0.93 (m, 13H), 0.93-0.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 46.94 (CH), 42.90 (CH), 41.42 (CH), 39.62 (CH), 35.95 (CH_2), 34.65 (CH_2), 33.13 (2·CH_2), 31.98 (CH_2), 28.13 (CH_2), 28.03 (2·CH_2), 11.29 (2·CH_3).
TOF MS EI+: Calcd. for $C_{14}H_{26}$: 194.2035; Found: 194.2040.

(*3R*,3aS*,6aR*)-Hexahydro-3-(iodomethyl)furo[2,3-*b*]furan (**21**)



1 mmol of 2-(allyloxy)-3-iodo-tetrahydrofuran was taken in 10 ml of distilled water stirred of 5 min; flushed with argon, added 0.1 ml solution of Et_3B (1.0 M in hexanes), allowed to stir at rt for 4.5 hrs. Then extracted with ethyl acetate (2×20 ml), combined organic extracts dried over Na_2SO_4, concentrated and purified by silica gel chromatography by using (Hexane: EtOAc = 8:2) as a eluent and **21** was obtained in 91% yield as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (d, *J* = 4.86 Hz, 1H), 4.03 (dd, *J* = 7.13 Hz, 1H), 3.90 (dd, *J* = 6.21 Hz, 2H), 3.46 (dd, *J* = 8.66, 8.57 Hz, 1H), 3.17 (dd, *J* = 9.81, 7.60 Hz, 1H), 3.08 (dd, *J* = 9.81, 8.36 Hz, 1H), 2.97-2.72 (m, 2H), 2.01-1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.99 (CH), 72.38 (CH_2), 69.34 (CH_2), 46.89 (CH), 45.68 (CH), 24.78 (CH_2), 0.76 (CH_2).
TOF MS EI$^+$: Calcd. for $C_7H_{11}IO_2$: 253.9804; Found: 253.9800.

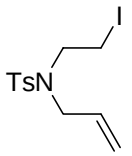
Hexahydro-3-methylfuro[2,3-*b*]furan (**22**)[199]



19a upon reaction with **2a** under $Ni(py)_4Cl_2$ catalysis gave mixture of **19a**, **21** and **22** in variable yields, Hexane: EtOAc = 8: 2 is used as a eluent for purification and **22** is obtained in 19% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, *J* = 5.0 Hz, 1H), 3.96-3.79 (m, 3H), 3.37 (dd, *J* = 11.3, 8.5 Hz, 1H), 2.83-2.69 (m, 1H), 2.47-2.33 (m, 1H), 1.96-1.75 (m, 2H), 1.02 (d, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.32 (CH), 74.21 (CH_2), 69.62 (CH_2), 46.90 (CH), 36.43 (CH), 25.47 (CH_2), 12.01 (CH_3).

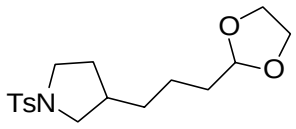
[199] Hackmann, C.; Schaefer, H. J. *Tetrahedron Lett.* **1993**, *49*, 4559-4574.

_N_-Allyl-_N_-(2-iodoethyl)-4-methylbenzenesulfonamide (23a)[200]



23a was prepared by general procedure by reaction of *N*-allyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide[201] with NaI. (Hexane: EtOAc = 20:1 is used as a eluent, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.71 (m, 2H), 7.39-7.32 (m, 2H), 5.72 (ddt, *J* = 16.3, 9.8, 6.4 Hz, 1H), 5.27-5.19 (m, 2H), 3.85-3.81 (m, 2H), 3.49-3.41 (m, 2H), 3.31-3.23 (m, 2H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.78 (C), 136.61 (C), 133.11 (CH), 130.20 (2·CH), 127.39 (2·CH), 120.01 (CH_2), 51.83 (CH_2), 50.45 (CH_2), 21.81 (CH_2), 1.84 (CH_2), 21.85(CH_3).

3-[3-(1,3-Dioxolan-2-yl)propyl)]-1-tosylpyrrolidine (24a)



Following general procedure **A** for cross-coupling, **24a** was obtained in 83% yield as pale yellow oil (Hexane: EtOAc = 7: 3 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.67 (m, 2H), 7.35-7.28 (m, 2H), 4.79 (t, *J* = 4.7 Hz, 1H), 3.98-3.79 (m, 4H), 3.43 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.38-3.13 (m, 2H), 2.77 (dd, *J* = 9.8, 8.0 Hz, 1H), 2.43 (s, 3H), 2.05-1.85 (m, 2H), 1.63-1.52 (m, 2H), 1.45-1.21 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.62 (C), 134.23 (C), 129.94 (2·CH), 127.85 (2·CH), 104.55 (CH), 65.20 (2·CH_2), 53.55 (CH_2), 47.90 (CH_2), 39.13 (CH), 34.08 (CH_2), 33.29 (CH_2), 31.74 (CH_2), 22.83 (CH_2), 21.85(CH_3).

FAB^{+}: Calcd. for $C_{17}H_{26}NO_4S$ (M^{+}+1): 340.158255. Found: 340.158400.

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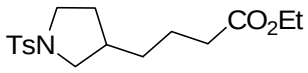
[200] (a) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565-1567; (b) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207-2213.

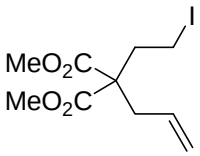
[201] Rai, K. M.; Lokanatha, A. *Heterocycles*, **1990**, *30*, 817-830.

Ethyl 4-(1-tosylpyrrolidin-3-yl)butanoate (**24a'**)



Following general procedure **A** for cross-coupling, **24a'** was obtained in 66% yield as pale yellow oil (Hexane: EtOAc = 6: 4 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.67 (m, 2H), 7.35-7.28 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.43 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.38-3.12 (m, 2H), 2.77(dd, *J* = 9.8, 8.0 Hz, 1H), 2.43 (s, 3H), 2.23 (t, *J* = 7.4 Hz, 2H), 2.06-1.86 (m, 3H), 1.58-1.47 (m, 2H), 1.40-1.25 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 173.57 (C), 143.65 (C), 134.06 (C), 129.93 (2·CH), 127.80 (2·CH), 60.62 (CH_2), 53.43 (CH_2), 47.83 (CH_2), 38.87 (CH), 34.40 (CH_2), 32.78 (CH_2), 31.62 (CH_2), 23.69 (CH_2), 21.82 (CH_3), 14.53 (CH_3).
FAB$^+$-MS. Calcd. for $C_{17}H_{26}NO_4S$ (M^++1): 340.158255. Found: 340.159600.

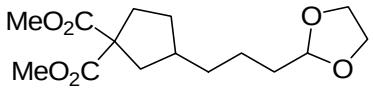
Dimethyl 2-allyl-2-(2-iodoethyl)malonate (**23b**)



Iodo compound **23b** was prepared by following the general procedure by reaction of dimethyl 2-allyl-2-(2-bromoethyl) malonate[202] and NaI. (Hexane: EtOAc = 9:1 is used as a eluent, 68% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (ddt, *J* = 16.9, 9.6, 5.3 Hz, 1H), 5.17-5.07 (m, 2H), 3.74 (s, 6H), 3.12-3.04 (m, 2H), 2.67-2.61 (m, 2H), 2.67-2.61 (m, 2H), 2.52-2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 170.51 (C), 132.12 (CH), 120.12 (CH_2), 59.12 (C), 52.65 (2·CH_3), 37.87 (CH_2), 37.65 (CH_2), -2.60 (CH_2).
Electronspray$^+$: Calcd. for $C_{10}H_{15}O_4I$ (M^++1): 327.0087; Found: 327.0094.

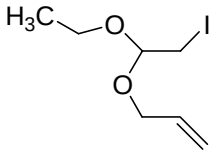
[202] Kuehne, M. E.; He, L.; Jokiel, P. A. Pace, C. J.; Fleck, M. W.; Maisonneuve, I. M.; Glick, S. D.; Bidlack, J. M. *J. Med. Chem.* **2003**, *46*, 2716-2730.

Dimethyl 3-[3-(1,3-dioxolan-2-yl)propyl]cyclopentane-1,1-dicarboxylate (**24b**)



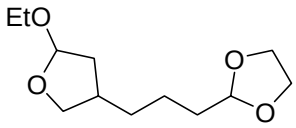
Following general procedure **A** for cross-coupling, **24b** was obtained in 64% yield as pale yellow oil (Hexane: EtOAc = 9: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (t, *J* = 4.8 Hz, 1H), 3.99-3.80 (m, 4H), 3.71 (s, 3H), 3.70 (s, 3H), 2.51-2.41 (m, 1H), 2.35-2.05 (m, 2H), 2.00-1.80 (m, 2H), 1.74-1.59 (m, 3H), 1.47-1.21 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 173.52 (C), 173.51 (C), 104.83 (CH), 65.17 (2·CH_2), 60.23 (C), 50.95 (CH_3), 52.93 (CH_3), 41.14 (CH_2), 40.10 (CH_2), 35.49 (CH_2), 34.33 (CH_2), 34.23 (CH_2), 32.44 (CH_2), 23.32 (CH_2).
FAB$^+$ MS: Calcd. for $C_{15}H_{25}O_6$ (M^++1): 301.165114; Found: 301.164100.

3-(1-Ethoxy-2-iodoethoxy)prop-1-ene (**23c**)



Iodoketal **23c** was prepared by following the general procedure for preparation of iodoketals, starting from ethylvinyl ether, NIS and allyl alcohol. (Hexane: EtOAc = 20:1 is used as a eluent, 91% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 16.1, 10.4, 5.8 Hz, 1H), 5.37-5.17 (m, 2H), 4.66 (t, *J* = 5.5 Hz, 1H), 4.19-4.00 (m, 2H), 3.73-3.51 (m, 2H), 3.23 (d, *J* = 5.5 Hz, 2H).

2-[3-(5-Ethoxy-tetrahydrofuran-3-yl)propyl]-1,3-dioxolane (**24c**)

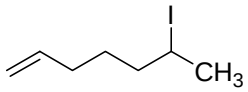


Following general procedure **A** for cross-coupling, **24c** was obtained in 55% yield as pale yellow oil (Hexane: EtOAc = 9: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14-5.08 (m, 1H), 4.83 (t, *J* = 4.8 Hz, 1H), 4.03-3.79 (m, 5H), 3.72 (dd, *J* = 7.1, 2.4 Hz, 1H), 3.51-3.38 (m, 2H), 2.33-2.03 (m, 2H), 1.72-1.60 (m, 4H), 1.19 (t, *J* = 7.0 Hz,

3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 105.26 (CH), 105.15 (CH), 72.54 (CH_2), 65.65 (2·CH_2), 63.78 (CH_2), 39.91 (CH_2), 39.46 (CH), 34.76 (CH_2), 33.79 (CH_2), 23.90 (CH_2), 16.08 (CH_3).

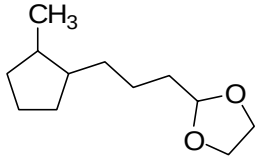
TOF MS EI$^+$: Calc. for $C_{12}H_{22}O_4$: 230.1518; Found 230.1526.

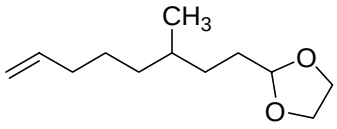
6-Iodohept-1-ene (**23d**)[203]



23d was prepared by following the general procedure for iodination of alcohols (see p 192) starting from hept-6-en-2-ol.[204] (Hexane: EtOAc = 50: 1 is used as a eluent, 72% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.07-4.93 (m, 2H), 4.25-4.12 (m, 1H), 2.15-1.99 (m, 2H), 1.92 (d, *J* = 6.86 Hz, 3H), 1.86-1.40 (m, 4H).

Mixture of 2-(3-(2-methylcyclopentyl)propyl)-1,3-dioxolane (**24d**), 55% yield, and **2-(3-methyloct-7-enyl)-1,3-dioxolane**, 29% yield.





General procedure was followed for cross-coupling, mixture of products were obtained as a colourless oil (Hexane: EtOAc = 20: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.0, 6.6 Hz, 1H), 5.03-4.88 (m, 2H), 4.84 (t, *J* = 4.8 Hz, 1H), 4.82 (t, *J* = 4.8 Hz, 1H), 4.01-3.81 (m, 9H), 2.07-1.91 (m, 3.5H), 1.79-1.55 (m, 10.5H), 1.50-1.07 (m, 19.1H), 0.87 (d, *J* = 6.4 Hz, 3.9H), 0.76 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR 75 MHz, $CDCl_3$, DEPT-135) δ 139.53 (CH), 114.59 (CH_2), 105.37 (CH), 105.12 (CH), 65.22 (2·CH_2), 43.70 (CH), 36.70 (CH_2), 36.30 (CH), 34.69 (CH_2), 34.45 (CH_2), 33.92 (CH_2), 32.97 (CH), 31.88 (CH_2), 31.39 (CH_2), 30.85 (CH_2), 30.05 (CH_2), 26.70 (CH_2), 23.70 (CH_2), 22.87 (CH_2), 19.89 (CH_3), 15.17 (CH_3).

TOF MS EI$^+$: Calc. for $C_{12}H_{22}O_2$: 197.1542; Found 197.1535.

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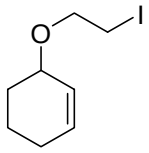
[203] Ashby, M. T.; Coleman, D. *J. Org. Chem.* **1987**, *52*, 4554-4564.

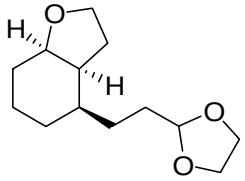
[204] Baillif, V.; Robins, R. J.; Billault, I.; Lesot, P. *J. Am. Chem. Soc.* **2006**, *128*, 11180-11187.

3-(2-Iodoethoxy)cyclohex-1-ene (**23e**)



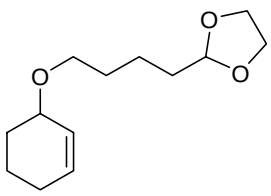
Preparation of **23e** is previously described by the reaction of 3-bromo cyclohexene, ethylene glycol and Na, to afford corresponding alcohol [2-(cyclohex-2-enyloxy)ethanol, 81% yield].[205] This alcohol is further subjected for iodination (see p 192) to afford **23e** as per the general procedure described above. (Hexane: EtOAc = 20: 1 is used as a eluent, 73% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87-5.69 (m, 2H), 3.92-3.83 (m, 1H), 3.78-3.63 (m, 2H), 3.20 (t, *J* = 7.1 Hz, 2H), 2.17-1.82 (m, 2H), 1.79-1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 131.53 (CH), 127.60 (CH), 73.32 (CH), 69.26 (CH_2), 28.60 (CH_2), 25.39 (CH_2), 19.32 (CH_2), 4.12 (CH_2).
TOF MS EI+: Calcd. for $C_8H_{13}OI$: 252.0011; Found: 252.0020.

(*3aS*,4R*,7aR)-4-[2-(1,3-Dioxalan-2yl)ethyl]octahydrobenzofuran** (**24e**).



Following general procedure **A** for cross-coupling, **24e** was obtained in 46% yield as colourless oil (Hexane: EtOAc = 9: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (t, *J* = 4.6 Hz, 1H), 3.99-3.73 (m, 7H), 2.09-1.39 (m, 11H), 1.19-0.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 105.19 (CH), 77.91 (CH), 66.27 (CH_2), 65.21 (2·CH_2), 43.97 (CH_2), 37.06 (CH), 31.64 (CH_2), 31.23 (CH_2), 30.33 (CH_2), 29.37 (CH_2), 28.62 (CH_2), 20.53 (CH_2).
TOF MS EI+: Calcd. for $C_{13}H_{22}O_3$: 226.1569; Found: 226.1564.

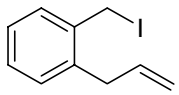
2-[(4-Cyclohex-2-enyloxy)butyl]-1,3-dioxolane.



[205] Baguley, P. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans I* **1998**, *13*, 2073-2082.

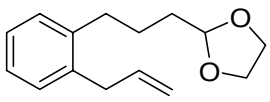
Following general procedure **A** for cross-coupling, **24e** was obtained in 36% yield as colourless oil (Hexane: EtOAc = 9: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.70 (m, 2H), 4.84 (t, *J* = 4.8 Hz, 1H), 3.98-3.77 (m, 5H), 3.54-3.38 (m, 2H), 2.11-1.41 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 130.92 (CH), 128.40 (CH), 104.92 (CH), 73.15 (CH), 68.35 (CH_2), 65.17 (2·CH_2), 34.06 (CH_2), 30.43 (CH_2), 28.69 (CH_2), 25.69 (CH_2), 21.22 (CH_2), 19.65 (CH_2).
TOF MS EI^{+}: Calc. for $C_{13}H_{22}O_3$: 226.1569; Found 225.1526.

1-Allyl-2-(iodomethyl)benzene (**25a**)[206]



Preparation of **25a** is previously described by stepwise synthesis, first the protection of 2-bromobenzyl alcohol with DHP (3,4-dihydro-2*H*-pyran), followed by Grignard reaction with allyl bromide and deprotection. The corresponding alcohol (2-(cyclohex-2-enyloxy)ethanol), this alcohol on reaction with PPh_3, Imidazole and I_2 gave **25a** in 46% yield as colourless oil (Hexane: EtOAc = 40: 1 is used as a eluent).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-6.99 (m, 4H), 5.93 (ddt, *J* = 16.7, 10.3, 6.2 Hz, 1H), 5.05-4.88 (m, 2H), 4.38 (br s, 2H), 3.39 (d, *J* = 6.1, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 138.54 (C), 137.36 (C), 136.49 (CH), 130.71 (CH), 130.40 (CH), 128.95 (CH), 127.36 (CH), 116.65 (CH_2), 37.26 (CH_2), 4.64 (CH_2).
TOF MS EI+: Calcd. for $C_{10}H_{11}I$: 275.9906; Found: 257.9902.

2-[3-(2-Allylphenyl)propyl]-1,3-dioxolane (**26a**)



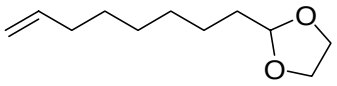
Following general procedure **A** for cross-coupling, **26a** was obtained in 82 % yield as colourless oil (Hexane: EtOAc = 20: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.12 (m, 4H), 5.96 (ddt, *J* =16.5, 10.2, 6.3 Hz, 1H), 5.06 (dm, *J* = 10.0, 1.8 Hz,

[206] Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507-2508.

1H), 5.00 (dm, *J* = 16.9, 1.8 Hz, 1H), 4.02-3.81 (m, 4H), 3.40 (dt, *J* = 6.4, 1.6 Hz, 2H), 2.71-2.62 (m, 2H), 1.78-1.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 140.59 (C), 137.88 (C), 137.70 (CH), 129.91 (CH), 129.56 (CH), 126.67 (CH), 126.41 (CH), 115.95 (CH_2), 104.77 (CH), 65.20 (2·CH_2), 37.36 (CH_2), 34.05 (CH_2), 32.81 (CH_2), 25.49 (CH_2).

TOF MS EI+: Calcd. for $C_{15}H_{20}O_2$: 232.1463; Found: 232.1470.

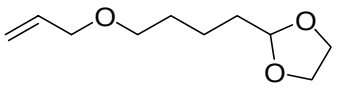
2-(Oct-7-enyl)-1,3-dioxolane (**26b**)



Following general procedure **A** for cross-coupling, **26b** was obtained in 41% yield as colourless oil (Hexane: EtOAc = 20: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 1H), 5.02-4.87 (m, 2H), 4.83 (t, *J* = 4.8 Hz, 1H), 3.99-3.80 (m, 4H), 2.07-1.97 (m, 2H), 1.66-1.60 (m, 2H), 1.41-1.28 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 139.49 (CH), 114.54 (CH_2), 105.03 (CH), 65.19 (2·CH_2), 34.25 CH_2), 34.12 (CH_2), 29.74 (CH_2), 29.37 (CH_2), 29.14 (CH_2), 24.39 (CH_2).

2-[4-(Allyloxy)butyl]-1,3-dioxolane (**26c**)

11 h, (Hexane: EtOAc = 10: 1), faint yellow oily liquid (22 mg, 25 %).

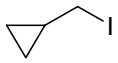


Following general procedure **A** for cross-coupling, **26c** was obtained in 25% yield as pale yellow oil (Hexane: EtOAc = 10: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, *J* =16.0, 10.4, 5.6 Hz, 1H), 5.25 (dm, *J* = 17.3, 1.6 Hz, 1H), 5.15 (dm, *J* = 10.4, 1.4 Hz, 1H), 4.84 (t, *J* = 4.7 Hz, 1H), 3.97-3.80 (m, 6H), 3.42 (t, *J* = 6.5 Hz, 2H), 1.66-1.44 (m, 4H), 0.95-0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 135.41 (CH), 117.09 (CH_2), 104.92 (CH), 72.18 CH_2), 70.54 (CH_2), 65.21 (2·CH_2), 34.03 (CH_2), 29.97 (CH_2), 21.13 (CH_2).

TOF MS EI+: Calcd. for $C_{10}H_{18}O_3$: 186.1256; Found: 186.1241.

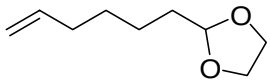
(Iodomethyl)cyclopropane (**25d**)

25d was prepared by following general procedure for iodination of alcohol (see p 192), i.e. cyclopropyl methanol.



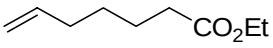
^{1}H NMR (300MHz, $CDCl_3$) δ 3.14 (d, *J* = 7.70Hz, 2H), 0.92-0.77 (m, 3H), 0.37-0.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 16.27 (CH), 14.33 (CH_2), 11.27 ($2{\cdot}CH_2$).
TOF MS EI+: Calcd. for C_4H_7I: 181.9593; Found: 181.9601.

2-(Hex-5-enyl)-1,3-dioxolane (**26d**)



Following general procedure **A** for cross-coupling, **26d** was obtained in 63% yield as colourless oil (Hexane: EtOAc = 20: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (ddt, *J* =17.0, 10.3, 6.7 Hz, 1H), 5.02 (dm, *J*=17.1, 1.7 Hz, 1H), 4.94 (dm, *J*=10.7, 1.2 Hz, 1H), 4.83 (t, *J* = 4.8 Hz, 1H), 3.98-3.80 (m, 4H), 2.11-2.01 (m, 2H), 1.07-1.61 (m, 2H), 1.48-1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 139.15 (CH), 114.4 (CH_2), 104.99 (CH), 65.2 ($2{\cdot}CH_2$), 34.12 CH_2), 34.05 (CH_2), 29.20 (CH_2), 23.95 (CH_2).
TOF MS EI+: Calcd. for $C_9H_{16}O_2$: 156.1150; Found: 155.1136.

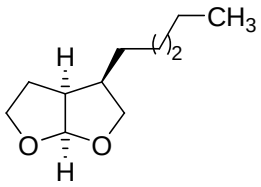
Ethyl hept-6-enoate (**26d'**)



Following general procedure **A** for cross-coupling, **26d'** was obtained in 59% yield as colourless oil (Hexane: EtOAc = 20: 1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.03-4.91 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.10-2.01 (m, 2H), 1.69-1.57 (m, 2H), 1.47-1.35 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.07 (C), 138.81 (CH), 115.02 (CH_2), 60.55 (CH_2), 34.57 CH_2), 33.73 (CH_2), 28.73 (CH_2), 24.85 (CH_2), 14.61 (CH_3).

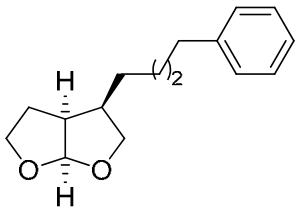
TOF MS EI+: Calcd. for $C_9H_{16}O_2$: 156.1150; Found: 155.1154.

(*3R,3aS,6aR*)-3-Pentylhexahydrofuro[2,3-*b*]furan (**28a**)



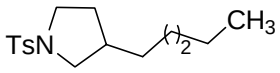
Following general procedure **B** for cross-coupling, **28a** was obtained in 65% yield as colourless oil (Hexane: EtOAc = 15:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 5.0 Hz, 1H), 3.89-3.81 (m, 3H), 3.48-3.37 (m, 1H), 2.78-2.65 (m, 1H), 2.38-2.25 (m, 1H), 1.89-1.78 (m, 2H), 1.48-1.21 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 110.13 (CH), 73.10 (CH_2), 69.51 (CH_2), 45.79 (CH), 42.55 (CH), 32.39 (CH_2), 28.55 (CH_2), 27.87 (CH_2), 25.31 (CH_2), 22.91 (CH_2), 14.41 (CH_3).
TOF MS EI+: Calcd. for $C_{11}H_{20}O_2$: 184.1464; Found: 184.1463.

(*3R,3aS,6aR*)-3-(4-Phenylbutyl)hexahydrofuro[2,3-*b*]furan (**28a'**)



Following general procedure **B** for cross-coupling, **28a'** was obtained in 58% yield as colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.12 (m, 5H), 5.71 (d, *J* = 5.1 Hz, 1H), 3.96-3.81 (m, 3H), 3.45-3.35 (m, 1H), 2.82-2.71 (m, 1H), 2.66-2.57 (m, 2H), 2.46-2.23 (m, 1H), 1.90-1.78 (m, 2H), 1.72-1.57 (m, 2H), 1.47-1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 142.78 (C), 128.74 (4·CH), 126.18 (CH), 110.18 (CH), 73.06 (CH_2), 69.54 (CH_2), 45.86 (CH), 42.55 (CH), 36.19 (CH_2), 31.98 (CH_2), 28.52 (CH_2), 27.84 (CH_2), 25.36 (CH_2).
TOF MS EI+: Calcd. for $C_{16}H_{23}O_2$: 247.1698; Found: 247.1669.

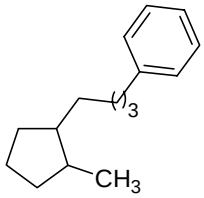
3-Pentyl-1-tosylpyrrolidine (**29a**)



Following general procedure **B** for cross-coupling, **29a** was obtained in 59% yield as pale yellow oil (Hexane: EtOAc = 15:2 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.67 (m, 2H), 7.36-7.29 (m, 2H), 3.48-3.13 (m, 3H), 2.76 (dd, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 2.06-1.84 (m, 2H), 1.40-1.10 (m, 9H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.64 (C), 134.66 (C), 129.60 (2·CH), 127.95 (2·CH), 53.72 (CH_2), 48.01 (CH_2), 39.49 (CH), 33.47 (CH_2), 32.41 (CH_2), 31.95 (CH_2), 28.17 (CH_2), 22.92 (CH_2), 14.41 (CH_3).

TOF MS EI+: Calcd. for $C_{16}H_{25}NO_2S$: 295.1606; Found: 295.1611.

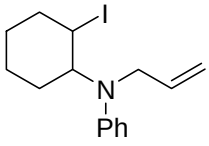
(4-(2-Methylcyclopentyl)butyl)benzene (**29b**)



Following general procedure **B** for cross-coupling, **29b** was obtained in 54% yield as colourless oil (Hexane: EtOAc = 40:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.16 (m, 5H), 2.68-2.61 (m, 2H), 2.09-1.93 (m, 1H), 1.88-1.47 (m, 7H), 1.43-1.15 (m, 5H), 1.02.0.95 (m, 1H), 0.80 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 143.41 (C), 128.81 (2·CH), 128.61 (2·CH), 125.94 (CH), 43.70 (CH), 36.44 (CH_2), 36.35 (CH), 33.93 (CH_2), 32.32 (CH_2), 30.74 (CH_2), 30.11 (CH_2), 28.90 (CH_2), 22.87 (CH_2), 15.17 (CH_3).

TOF MS EI+: Calcd. for $C_{16}H_{24}$: 218.1876; Found: 218.1880.

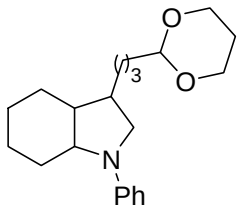
***N*-Allyl-*N*-(2-iodocyclohexyl)benzenamine** (**27c**)



27c is prepared by following the general procedure described above (see p 192) starting from corresponding alcohol (2-(allyl(phenyl)amino)cyclohexanol),[207] (Hexane: EtOAc = 30:1 is used as a eluent, 63% yield).

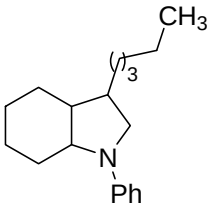
^{1}H NMR (75 MHz, $CDCl_3$) δ 7.25-6.62 (m, 5H), 5.95-7.76 (m, 1H), 5.22-5.03 (m, 2H), 4.25-4.19 (m, 1H), 3.95-3.79 (m, 2H), 2.68-2.59 (m, 1H), 2.21-2.02 (m, 1H), 1.92-1.81 (m, 2H), 1.63-1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 148.65 (C), 136.87 (CH), 129.11 (2·CH), 117.84 (CH), 116.70 (CH), 115.37 (2·CH), 66.50 (CH), 47.03 (CH_2), 41.13 (CH_2), 36.07 (CH), 31.24 (CH_2), 28.82 (CH_2), 25.97 (CH_2).

3-[3-(1,3-Dioxan-2-yl)propyl]-1-phenyloctahydro-1*H*-indole (**29c**)



Following general procedure **B** for cross-coupling, **29c** was obtained in 61% yield as colourless oil (Hexane: EtOAc = 10:1 is used as a eluent): ^{1}H NMR (75 MHz, $CDCl_3$) δ 7.28-7.16 (m, 2H), 6.79-6.51 (m, 3H), 4.58-4.49 (m, 1H), 4.19-4.07 (m, 2H), 3.85-3.69 (m, 3H), 3.59-3.27 (m, 2H), 2.40-2.22 (m, 1H), 2.20-1.99 (m, 3H), 1.79-1.57 (m, 5H), 1.55-1.10 (m, 9H); Most signals overlap, so there is a possibily of two stereoisomers, ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 150.09 (C), 147.22 (C), 129.55 (CH), 128.97 (2·CH), 116.65 (CH), 114.99 (2·CH), 111.38 (CH), 102.58 (CH), 67.26 (2·CH_2), 58.69 (CH), 58.11 (CH), 57.87 (CH_2), 53.44 (CH_2), 43.76 (CH), 41.82 (CH), 41.07 (CH), 38.01 (CH), 35.96 (CH_2), 35.82 (CH_2), 33.31 (CH_2), 28.12 (CH_2), 27.44 (CH_2), 26.78 (CH_2), 26.22 (CH_2), 25.17 (CH_2), 25.08 (CH_2), 24.26 (CH_2), 23.21 (CH_2), 23.16 (CH_2), 23.06 (CH_2), 21.63 (CH_2), 21.46 (CH_2).

3-Pentyl-1-phenyloctahydro-1*H*-indole (**29c'**)



[207] Swamy, N. R.; Goud, T. V.; Reddy, S. M.; Krishnaiah, P.; Venkateswarlu, Y. *Synth. Commun*. **2004**, *34*, 727-734.

Following general procedure **B** for cross-coupling, **29c'** was obtained in 73% yield as colourless oil (Hexane: EtOAc = 20:1 is used as a eluent): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.14 (m, 2H), 6.72-6.62 (m, 3H), 3.77-3.69 (m, 1H), 3.48-3.25 (m, 2H), 2.35-2.22 (m, 1H), 2.18-1.96 (m, 2H), 1.65-1.49 (m, 3H), 1.45-1.15 (m, 12H), 0.88 (d, *J* = 6.6 Hz, 3H). Most signals overlap, so there is a possibily of two stereoisomers, ^{13}C NMR (75 MHz, $CDCl_3$, DEPT-135) δ 136.09 (C), 130.69 (C), 129.57 (2·CH), 129.00 (2·CH), 43.82 (CH), 37.99 (CH), 33.38 (CH), 32.59 (CH_2), 32.44 (CH_2), 28.47 (CH_2), 28.33 (CH_2), 28.14 (CH_2), 25.17 (CH_2), 23.01 (CH_2), 22.96 (CH_2), 21.64 (CH_2).
TOF MS EI+: Calcd. for $C_{19}H_{29}N$: 271.2300; Found: 271.2306.

COMPUTATIONAL SECTION

I. Computational methods[208]

Calculations were performed with Gaussian 03 at DFT level.[209] The geometries of all complexes here reported were optimized using the B3LYP hybrid functional.[210] Optimizations were carried out using the standard 6-31G(d) basis set for C, H, N and O. The LANL2DZ basis set, which includes the relativistic effective core potential (ECP) of Hay and Wadt and employs a split-valence (double-ζ) basis set, was used for Ni, Zn and I.[211] Harmonic frequencies were calculated at the same level to characterize the stationary points and to determine the zero-point energies (ZPE). The starting approximate geometries for the transition states (TS) were graphically located. Intrinsic reaction coordinate (IRC) studies were performed to confirm the relation of the transition states with the corresponding minima. PCM calculations in THF were performed on the optimized stationary points without geometry optimization.[212]

---

[208] The computational studies have been performed by Dr. D. J. Cárdenas and Dr. Elena Buñuel.

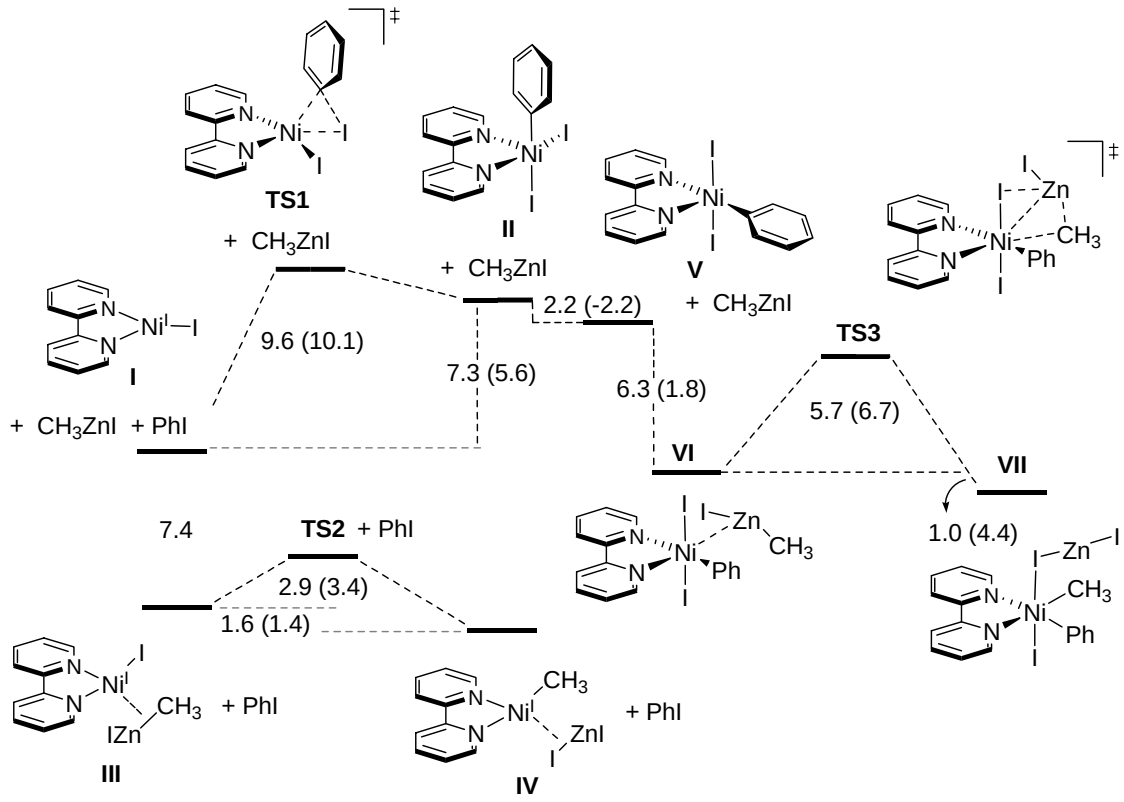
[209] Gaussian 03, Revision B.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 2003.

[210] (a) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627. (b) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974-12980. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283. (d) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 284-298. (e) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310.

[211] (a) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648- 5653. (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098-3100. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789

[212] Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027-2094.

II. Coordinates and energies for the stationary points included in the main text in the Ni^{I}-Ni^{III} catalytic cycle for the cross-coupling of $C(sp^2)$ electrophiles with alkylzinc halides



B3LYP/6-31G(d) (C, H, N), LANL2DZ (Ni, Zn, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets.

I

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.000000	0.000000	-2.466515
2	7	0	1.307078	0.000000	-0.932809
3	6	0	2.914797	0.000000	1.338688
4	6	0	0.740990	0.000000	0.299427
5	6	0	2.644805	0.000000	-1.041650
6	6	0	3.487588	0.000000	0.066266
7	6	0	1.526848	0.000000	1.456198
8	1	0	3.033294	0.000000	-2.055462
9	1	0	4.563770	0.000000	-0.071051
10	1	0	1.065781	0.000000	2.437494
11	1	0	3.537831	0.000000	2.227946
12	7	0	-1.307078	0.000000	-0.932809
13	6	0	-2.914797	0.000000	1.338688
14	6	0	-2.644805	0.000000	-1.041650
15	6	0	-0.740990	0.000000	0.299427

```
  16          6             0       -1.526848    0.000000    1.456198
  17          6             0       -3.487588    0.000000    0.066266
  18          1             0       -3.033294    0.000000   -2.055462
  19          1             0       -1.065781    0.000000    2.437494
  20          1             0       -4.563770    0.000000   -0.071051
  21          1             0       -3.537831    0.000000    2.227946
  22         53             0        0.000000    0.000000   -4.983578
 ---------------------------------------------------------------------

 Zero-point correction=                           0.160929
(Hartree/Particle)
 Thermal correction to Energy=                    0.173514
 Thermal correction to Enthalpy=                  0.174458
 Thermal correction to Gibbs Free Energy=         0.114822
 Sum of electronic and zero-point Energies=           -676.016589
 Sum of electronic and thermal Energies=              -676.004004
 Sum of electronic and thermal Enthalpies=            -676.003060
 Sum of electronic and thermal Free Energies=         -676.062696

-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -676.172372
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =    -676.201739
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =    -676.192234
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -18.43
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      25.29
 Dispersion energy                        (kcal/mol) =     -21.06
 Repulsion energy                         (kcal/mol) =       1.74
 Total non electrostatic                  (kcal/mol) =       5.96
 ---------------------------------------------------------------------
```

TS1

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0       -0.169056   -0.080319   -0.274899
    2         53             0       -1.021681   -2.027649   -1.877163
    3          6             0       -0.911958    0.233858    1.652168
    4          6             0        0.021621   -0.748488    4.091973
    5          6             0       -1.332595   -1.031053    2.096421
    6          6             0       -0.095589    1.042613    2.460353
    7          6             0        0.385847    0.534239    3.665785
    8          6             0       -0.837448   -1.522361    3.308300
    9          1             0        0.387696   -1.131115    5.040607
   10          1             0       -2.014051   -1.621967    1.494673
   11          1             0        0.171262    2.043772    2.138624
   12          1             0        1.040680    1.147704    4.279962
   13          1             0       -1.143046   -2.510288    3.643794
   14          7             0        1.716328   -0.874610    0.192607
   15          6             0        4.282178   -1.751399    0.780615
   16          6             0        1.916843   -2.105968    0.674090
   17          6             0        2.768584   -0.058270   -0.020485
   18          6             0        4.074215   -0.472909    0.268981
   19          6             0        3.186363   -2.587644    0.987030
```

```
   20          7             0        1.117896    1.538467   -0.740691
   21          6             0        3.014597    3.409796   -1.547531
   22          6             0        0.743545    2.703646   -1.287919
   23          6             0        2.436920    1.271500   -0.592826
   24          6             0        3.409501    2.197864   -0.987919
   25          6             0        1.654805    3.670471   -1.705322
   26          1             0        5.288694   -2.088689    1.010154
   27          1             0        1.026616   -2.714080    0.793401
   28          1             0        4.918151    0.186098    0.101636
   29          1             0        3.305551   -3.593412    1.375627
   30          1             0        3.760028    4.134439   -1.861588
   31          1             0       -0.326249    2.854461   -1.385292
   32          1             0        4.463525    1.973994   -0.874170
   33          1             0        1.299927    4.597120   -2.143658
   34         53             0       -2.480005    1.378753    0.270705
 ---------------------------------------------------------------------

 Zero-point correction=                           0.251292
(Hartree/Particle)
 Thermal correction to Energy=                    0.271161
 Thermal correction to Enthalpy=                  0.272105
 Thermal correction to Gibbs Free Energy=         0.197027
 Sum of electronic and zero-point Energies=           -918.932461
 Sum of electronic and thermal Energies=              -918.912592
 Sum of electronic and thermal Enthalpies=            -918.911648
 Sum of electronic and thermal Free Energies=         -918.986726

-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -919.176848
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -919.212178
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -919.196612
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -22.17
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      35.61
 Dispersion energy                        (kcal/mol) =     -28.11
 Repulsion energy                         (kcal/mol) =       2.26
 Total non electrostatic                  (kcal/mol) =       9.77
 ---------------------------------------------------------------------
```

II

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0        0.275742   -0.063870   -0.217761
    2         53             0       -0.260253   -2.507579   -1.213145
    3          6             0        0.858418    1.834764   -0.190485
    4          6             0        1.163309    4.588141   -0.512944
    5          6             0        1.266367    2.343680   -1.424050
    6          6             0        0.641937    2.680846    0.893943
    7          6             0        0.788415    4.062947    0.725164
    8          6             0        1.403364    3.727931   -1.585850
    9          1             0        1.283720    5.660997   -0.636754
   10          1             0        1.498954    1.681562   -2.255042
   11          1             0        0.365195    2.286086    1.866557
```

```
   12          1             0        0.612533    4.726152    1.569079
   13          1             0        1.718237    4.125443   -2.547777
   14          7             0       -1.588894    0.544522   -0.817741
   15          6             0       -4.176027    1.321789   -1.431510
   16          6             0       -1.905969    0.908654   -2.064809
   17          6             0       -2.530218    0.550080    0.149704
   18          6             0       -3.843960    0.939362   -0.135392
   19          6             0       -3.191016    1.307059   -2.418485
   20          7             0       -0.759831   -0.192236    1.579695
   21          6             0       -2.391434   -0.484001    3.800082
   22          6             0       -0.250195   -0.630858    2.737055
   23          6             0       -2.074052    0.104676    1.487238
   24          6             0       -2.919653   -0.032439    2.593051
   25          6             0       -1.033801   -0.789992    3.877908
   26          1             0       -5.191651    1.625228   -1.666736
   27          1             0       -1.102786    0.868927   -2.792232
   28          1             0       -4.598726    0.945167    0.641994
   29          1             0       -3.407581    1.592596   -3.442099
   30          1             0       -3.036157   -0.600041    4.666152
   31          1             0        0.810914   -0.858324    2.726583
   32          1             0       -3.975590    0.198041    2.515630
   33          1             0       -0.584736   -1.150441    4.797048
   34         53             0        2.779028   -0.442890    0.388946
 ---------------------------------------------------------------------
 Zero-point correction=                           0.252273
(Hartree/Particle)
 Thermal correction to Energy=                    0.272545
 Thermal correction to Enthalpy=                  0.273490
 Thermal correction to Gibbs Free Energy=         0.197833
 Sum of electronic and zero-point Energies=           -918.936202
 Sum of electronic and thermal Energies=              -918.915929
 Sum of electronic and thermal Enthalpies=            -918.914985
 Sum of electronic and thermal Free Energies=         -918.990642

-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -919.180619
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -919.219448
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -919.203520
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -24.37
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      35.77
 Dispersion energy                        (kcal/mol) =     -28.04
 Repulsion energy                         (kcal/mol) =       2.27
 Total non electrostatic                  (kcal/mol) =       9.99
 ---------------------------------------------------------------------
```

III

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0       -0.872214    0.080746   -0.766018
    2         53             0        1.004206    2.006717   -1.431658
    3          7             0       -2.632044   -1.021658   -0.643262
    4          6             0       -5.133442   -2.216511   -0.356751
```

```
    5          6             0       -3.456079   -0.638956    0.360750
    6          6             0       -3.040265   -1.978756   -1.490084
    7          6             0       -4.279335   -2.605519   -1.386867
    8          6             0       -4.717254   -1.222899    0.525187
    9          7             0       -1.757053    0.979722    0.863620
   10          6             0       -3.032008    1.880290    3.169901
   11          6             0       -1.220344    1.960360    1.604915
   12          6             0       -2.934952    0.433632    1.245195
   13          6             0       -3.595669    0.865153    2.399935
   14          6             0       -1.823091    2.441782    2.765304
   15          1             0       -6.110964   -2.674990   -0.241101
   16          1             0       -2.339351   -2.250247   -2.271826
   17          1             0       -4.559776   -3.374334   -2.098916
   18          1             0       -5.374293   -0.902038    1.324792
   19          1             0       -3.531052    2.222427    4.071600
   20          1             0       -0.281953    2.363618    1.238533
   21          1             0       -4.531693    0.412490    2.705209
   22          1             0       -1.346522    3.234466    3.332057
   23          6             0        0.332385   -1.681257   -1.873176
   24          1             0        1.131491   -1.921706   -2.589863
   25          1             0       -0.415462   -1.156586   -2.491641
   26          1             0       -0.084391   -2.620256   -1.499833
   27         30             0        1.567789   -0.677883   -0.508792
   28         53             0        3.391196   -1.221578    1.278920
 ---------------------------------------------------------------------
Zero-point correction=                           0.198175
(Hartree/Particle)
 Thermal correction to Energy=                    0.217744
 Thermal correction to Enthalpy=                  0.218688
 Thermal correction to Gibbs Free Energy=         0.141944
 Sum of electronic and zero-point Energies=           -792.925187
 Sum of electronic and thermal Energies=              -792.905618
 Sum of electronic and thermal Enthalpies=            -792.904674
 Sum of electronic and thermal Free Energies=         -792.981418

-----------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -793.118912
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -793.146638
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -793.130273
 -----------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -17.40
 -----------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      33.55
 Dispersion energy                        (kcal/mol) =     -25.29
 Repulsion energy                         (kcal/mol) =       2.01
 Total non electrostatic                  (kcal/mol) =      10.27
 -----------------------------------------------------------------
```

TS2

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0        0.897528   -0.423262   -0.482599
    2         53             0       -0.492798   -1.739853    1.623854
    3          7             0        2.914454   -0.586844   -0.736062
    4          6             0        5.692249   -0.557153   -0.958919
```

```
    5          6             0        3.617653    0.498129   -0.325928
    6          6             0        3.577052   -1.640489   -1.240628
    7          6             0        4.961219   -1.672647   -1.370600
    8          6             0        5.013153    0.537249   -0.431667
    9          7             0        1.468812    1.376733    0.280379
   10          6             0        2.509459    3.768251    1.255110
   11          6             0        0.662647    2.314870    0.802392
   12          6             0        2.805575    1.600646    0.240511
   13          6             0        3.351309    2.796604    0.721960
   14          6             0        1.136879    3.524552    1.300006
   15          1             0        6.774480   -0.539486   -1.044249
   16          1             0        2.964186   -2.483508   -1.546333
   17          1             0        5.448193   -2.549825   -1.783327
   18          1             0        5.567499    1.408891   -0.103865
   19          1             0        2.920965    4.699551    1.632422
   20          1             0       -0.396931    2.079585    0.821713
   21          1             0        4.420482    2.969720    0.685927
   22          1             0        0.442726    4.249868    1.710430
   23          6             0       -0.336502   -0.782667   -2.312379
   24          1             0       -1.222675   -1.184464   -2.830356
   25          1             0        0.415817   -1.578225   -2.429498
   26          1             0       -0.024126    0.093805   -2.887571
   27         30             0       -1.632049   -0.494223   -0.611198
   28         53             0       -3.886578    0.827755   -0.553400
 ---------------------------------------------------------------------

 Zero-point correction=                           0.197037
(Hartree/Particle)
 Thermal correction to Energy=                    0.216151
 Thermal correction to Enthalpy=                  0.217096
 Thermal correction to Gibbs Free Energy=         0.141659
 Sum of electronic and zero-point Energies=           -792.920616
 Sum of electronic and thermal Energies=              -792.901501
 Sum of electronic and thermal Enthalpies=            -792.900557
 Sum of electronic and thermal Free Energies=         -792.975993
-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                   (a.u.) =    -793.111948
 <psi(f)|H+V(f)/2|psi(f)>                  (a.u.) =    -793.141229
 Total free energy in solution:
  with all non electrostatic terms         (a.u.) =    -793.122484
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -18.37
 ---------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      34.72
 Dispersion energy                       (kcal/mol) =     -24.95
 Repulsion energy                        (kcal/mol) =       2.00
 Total non electrostatic                 (kcal/mol) =      11.76
 ---------------------------------------------------------------------
```

IV

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0       -0.857776   -0.148905    0.771277
    2         53             0        0.456636   -2.637990   -0.240960
    3          7             0       -2.727782   -0.549887    0.050416
    4          6             0       -5.377543   -0.854715   -0.742434
```

```
    5          6             0       -3.471554    0.538508   -0.259031
    6          6             0       -3.278683   -1.769152   -0.041587
    7          6             0       -4.601137   -1.969120   -0.430974
    8          6             0       -4.806032    0.412984   -0.658610
    9          7             0       -1.508238    1.777827    0.340958
   10          6             0       -2.581257    4.229227   -0.420443
   11          6             0       -0.788390    2.903085    0.447612
   12          6             0       -2.767407    1.841744   -0.149851
   13          6             0       -3.332109    3.061466   -0.537662
   14          6             0       -1.282485    4.152467    0.078942
   15          1             0       -6.413081   -0.966762   -1.049576
   16          1             0       -2.619054   -2.598049    0.192424
   17          1             0       -5.002168   -2.975331   -0.489469
   18          1             0       -5.397133    1.289166   -0.898170
   19          1             0       -3.005048    5.182433   -0.721964
   20          1             0        0.217889    2.786814    0.836375
   21          1             0       -4.338735    3.104246   -0.936897
   22          1             0       -0.658298    5.033941    0.178929
   23          6             0        0.623397    0.258491    2.319055
   24          1             0        1.398809   -0.311708    2.854208
   25          1             0       -0.311245   -0.072495    2.808979
   26          1             0        0.769268    1.314854    2.565391
   27         30             0        1.631324   -0.231001    0.468882
   28         53             0        3.695594    1.013212   -0.539647
 ---------------------------------------------------------------------
 Zero-point correction=                           0.197971
(Hartree/Particle)
 Thermal correction to Energy=                    0.217550
 Thermal correction to Enthalpy=                  0.218494
 Thermal correction to Gibbs Free Energy=         0.142359
 Sum of electronic and zero-point Energies=           -792.927746
 Sum of electronic and thermal Energies=              -792.908167
 Sum of electronic and thermal Enthalpies=            -792.907223
 Sum of electronic and thermal Free Energies=         -792.983358

-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                   (a.u.) =    -793.121467
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =    -793.148813
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =    -793.132133
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -17.16
 ---------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      33.65
 Dispersion energy                       (kcal/mol) =     -25.18
 Repulsion energy                        (kcal/mol) =       1.99
 Total non electrostatic                 (kcal/mol) =      10.47
 ---------------------------------------------------------------------
```

V

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0        0.209951    0.141990   -0.185434
    2         53             0       -0.045797   -1.877848   -1.938913
    3          6             0        2.146280   -0.150554    0.142750
```

```
    4          6             0        4.833231   -0.691215    0.691217
    5          6             0        3.028822   -0.396091   -0.908596
    6          6             0        2.608214   -0.113394    1.459230
    7          6             0        3.950864   -0.406724    1.732428
    8          6             0        4.371148   -0.673957   -0.625618
    9         53             0        0.724372    2.693153    0.282966
   10          1             0        5.877044   -0.908151    0.902157
   11          1             0        2.688374   -0.403850   -1.936875
   12          1             0        1.953776    0.173720    2.276035
   13          1             0        4.303494   -0.378591    2.760808
   14          1             0        5.050524   -0.888438   -1.447013
   15          7             0       -0.688412   -0.932383    1.394507
   16          6             0       -2.114891   -2.334848    3.325327
   17          6             0       -0.070043   -1.805808    2.198983
   18          6             0       -2.026983   -0.765851    1.498118
   19          6             0       -2.765427   -1.451488    2.468966
   20          6             0       -0.742813   -2.527427    3.181875
   21          7             0       -1.799533    0.598462   -0.450562
   22          6             0       -4.495642    1.236025   -0.574921
   23          6             0       -2.642883    0.124153    0.487690
   24          6             0       -2.269300    1.364397   -1.442566
   25          6             0       -3.614814    1.702173   -1.550082
   26          6             0       -4.006612    0.439311    0.455658
   27          1             0       -2.676552   -2.874494    4.081986
   28          1             0        0.995412   -1.922091    2.040431
   29          1             0       -3.836857   -1.311424    2.546919
   30          1             0       -0.196978   -3.222690    3.810458
   31          1             0       -5.551224    1.487512   -0.615251
   32          1             0       -1.535981    1.715800   -2.159824
   33          1             0       -3.954312    2.320673   -2.373774
   34          1             0       -4.679121    0.070389    1.220894
 ---------------------------------------------------------------------
Zero-point correction=                           0.252758
(Hartree/Particle)
Thermal correction to Energy=                    0.272905
Thermal correction to Enthalpy=                  0.273849
Thermal correction to Gibbs Free Energy=         0.198252
Sum of electronic and zero-point Energies=           -918.939718
Sum of electronic and thermal Energies=              -918.919570
Sum of electronic and thermal Enthalpies=            -918.918626
Sum of electronic and thermal Free Energies=         -918.994224

---------------------------------------------------------------------

 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -919.185809
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -919.215891
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -919.200668
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -18.88
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      35.70
 Dispersion energy                        (kcal/mol) =     -28.41
 Repulsion energy                         (kcal/mol) =       2.27
 Total non electrostatic                  (kcal/mol) =       9.55
 ---------------------------------------------------------------------
```

VI

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	1.157944	0.201129	-0.101767
2	6	0	-0.286332	1.516297	0.263792
3	6	0	-2.341864	3.325612	0.844406
4	6	0	-1.013644	2.097217	-0.778497
5	6	0	-0.606300	1.803773	1.590986
6	6	0	-1.624583	2.722465	1.876812
7	6	0	-2.042176	3.003354	-0.478661
8	1	0	-3.142242	4.024155	1.069472
9	1	0	-0.770783	1.897483	-1.814839
10	1	0	-0.120610	1.287615	2.411955
11	1	0	-1.875825	2.929952	2.913756
12	1	0	-2.592103	3.465263	-1.294587
13	7	0	2.604785	0.521465	1.384319
14	6	0	4.686959	0.774389	3.205233
15	6	0	2.654620	1.566056	2.219722
16	6	0	3.603137	-0.391682	1.396290
17	6	0	4.656222	-0.292819	2.311703
18	6	0	3.676022	1.731362	3.151807
19	7	0	2.512323	-1.299695	-0.527664
20	6	0	4.321634	-3.374524	-0.839634
21	6	0	3.529216	-1.435748	0.348039
22	6	0	2.390025	-2.154252	-1.550266
23	6	0	3.278490	-3.206540	-1.749427
24	6	0	4.451049	-2.480586	0.219418
25	1	0	5.499201	0.863362	3.920300
26	1	0	1.851286	2.286915	2.125734
27	1	0	5.451231	-1.028674	2.318365
28	1	0	3.672539	2.592998	3.810459
29	1	0	5.028979	-4.190472	-0.952633
30	1	0	1.552022	-1.983596	-2.217775
31	1	0	3.145806	-3.875959	-2.592232
32	1	0	5.258332	-2.598961	0.932441
33	53	0	2.319949	1.785979	-1.883010
34	53	0	-0.496896	-1.690688	0.837720
35	6	0	-2.017228	-0.788187	-2.878923
36	30	0	-2.823124	-0.568913	-1.033882
37	53	0	-4.932467	-0.336311	0.517148
38	1	0	-1.999142	-1.850917	-3.146882
39	1	0	-0.991077	-0.404956	-2.908996
40	1	0	-2.608606	-0.253904	-3.630463

```
 Zero-point correction=                           0.289545
(Hartree/Particle)
 Thermal correction to Energy=                    0.317265
 Thermal correction to Enthalpy=                  0.318209
 Thermal correction to Gibbs Free Energy=         0.220271
 Sum of electronic and zero-point Energies=          -1035.846607
 Sum of electronic and thermal Energies=             -1035.818887
 Sum of electronic and thermal Enthalpies=           -1035.817943
 Sum of electronic and thermal Free Energies=        -1035.915880

-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1036.129894
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1036.163482
```

```
Total free energy in solution:
 with all non electrostatic terms            (a.u.) =   -1036.136329
-------------------------------------------------------------------
(Polarized solute)-Solvent               (kcal/mol) =     -21.08
-------------------------------------------------------------------
Cavitation energy                        (kcal/mol) =      46.16
Dispersion energy                        (kcal/mol) =     -31.57
Repulsion energy                         (kcal/mol) =       2.45
Total non electrostatic                  (kcal/mol) =      17.04
-------------------------------------------------------------------
```

TS3

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.740598	0.196952	-0.237211
2	6	0	-0.659474	1.470005	0.500404
3	6	0	-2.475096	3.269257	1.661285
4	6	0	-1.238159	2.488416	-0.273671
5	6	0	-1.000374	1.353587	1.857266
6	6	0	-1.905257	2.256350	2.430823
7	6	0	-2.146263	3.377847	0.309676
8	1	0	-3.184140	3.960414	2.108017
9	1	0	-0.983604	2.599887	-1.319857
10	1	0	-0.604061	0.548520	2.464838
11	1	0	-2.176363	2.140066	3.476816
12	1	0	-2.589700	4.158055	-0.302813
13	7	0	2.226512	0.326574	1.288639
14	6	0	4.361409	0.360819	3.068066
15	6	0	2.234752	1.168914	2.327790
16	6	0	3.283355	-0.489876	1.086937
17	6	0	4.367518	-0.496492	1.971922
18	6	0	3.278811	1.218110	3.247821
19	7	0	2.166290	-1.126254	-0.944301
20	6	0	4.120212	-2.974019	-1.652127
21	6	0	3.232445	-1.322240	-0.135448
22	6	0	2.067341	-1.824391	-2.082193
23	6	0	3.022063	-2.755813	-2.479603
24	6	0	4.225233	-2.249654	-0.468861
25	1	0	5.196822	0.365608	3.761628
26	1	0	1.377082	1.824476	2.415310
27	1	0	5.214172	-1.151236	1.805689
28	1	0	3.237010	1.917053	4.076176
29	1	0	4.885102	-3.696537	-1.919970
30	1	0	1.194036	-1.627669	-2.689804
31	1	0	2.894549	-3.293954	-3.412490
32	1	0	5.071466	-2.410162	0.187606
33	53	0	2.058839	2.236230	-1.483253
34	53	0	-0.373037	-2.145466	1.076145
35	6	0	-0.870710	-0.179758	-2.336430
36	30	0	-1.970128	-0.399344	-0.551316
37	53	0	-4.570738	-0.484164	-0.270851
38	1	0	-0.926848	-1.180546	-2.780922
39	1	0	0.113771	0.252482	-2.526730
40	1	0	-1.587012	0.480782	-2.842622

```
 Zero-point correction=                           0.290125
(Hartree/Particle)
 Thermal correction to Energy=                    0.316301
 Thermal correction to Enthalpy=                  0.317245
 Thermal correction to Gibbs Free Energy=         0.227727
 Sum of electronic and zero-point Energies=          -1035.837581
 Sum of electronic and thermal Energies=             -1035.811405
 Sum of electronic and thermal Enthalpies=           -1035.810461
 Sum of electronic and thermal Free Energies=        -1035.899979

-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1036.119653
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1036.152754
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -1036.131746
 -------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -20.77
 -------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      42.23
 Dispersion energy                        (kcal/mol) =     -31.50
 Repulsion energy                         (kcal/mol) =       2.46
 Total non electrostatic                  (kcal/mol) =      13.18
 -------------------------------------------------------------------
```

VII

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.800815	0.223836	-0.323975
2	7	0	1.975547	0.145014	1.358022
3	6	0	3.734331	-0.159042	3.495681
4	6	0	1.939879	0.984633	2.400931
5	6	0	2.912781	-0.831614	1.331687
6	6	0	3.798990	-1.011728	2.398425
7	6	0	2.795511	0.868956	3.492526
8	7	0	2.120738	-1.248244	-0.891111
9	6	0	3.899960	-3.346454	-1.324046
10	6	0	2.971495	-1.629070	0.090183
11	6	0	2.167127	-1.877072	-2.071157
12	6	0	3.040419	-2.927745	-2.335669
13	6	0	3.866839	-2.686163	-0.099995
14	53	0	2.738299	2.162391	-1.303629
15	6	0	-0.535962	1.533585	0.366496
16	6	0	-2.054137	3.591835	1.592084
17	6	0	-0.773731	2.760706	-0.292188
18	6	0	-1.107123	1.365067	1.653611
19	6	0	-1.857550	2.384075	2.257620
20	6	0	-1.510257	3.777376	0.316544
21	53	0	-0.887733	-2.316011	0.668400
22	1	0	4.417517	-0.288494	4.329552
23	1	0	1.202456	1.774458	2.351658
24	1	0	4.542519	-1.798645	2.370069
25	1	0	2.721948	1.576007	4.311620
26	1	0	4.589716	-4.169634	-1.483083
27	1	0	1.481040	-1.528189	-2.831947

```
  28          1             0        3.033653   -3.401391   -3.311229
  29          1             0        4.533371   -2.993211    0.696470
  30          1             0       -2.638881    4.381513    2.055513
  31          1             0       -0.347269    2.933964   -1.274516
  32          1             0       -0.961054    0.432334    2.193134
  33          1             0       -2.289637    2.219276    3.240794
  34          1             0       -1.661765    4.716675   -0.208246
  35          6             0       -0.173432    0.189971   -2.072640
  36         30             0       -2.030069   -0.014587   -0.369571
  37         53             0       -4.618732   -0.232426   -0.411079
  38          1             0       -0.460244   -0.837530   -2.317392
  39          1             0        0.658190    0.523505   -2.696894
  40          1             0       -0.994335    0.888684   -2.281670
 ---------------------------------------------------------------------

 Zero-point correction=                           0.291872
(Hartree/Particle)
 Thermal correction to Energy=                    0.318343
 Thermal correction to Enthalpy=                  0.319287
 Thermal correction to Gibbs Free Energy=         0.228094
 Sum of electronic and zero-point Energies=          -1035.848316
 Sum of electronic and thermal Energies=             -1035.821846
 Sum of electronic and thermal Enthalpies=           -1035.820902
 Sum of electronic and thermal Free Energies=        -1035.912094

---------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1036.134041
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =   -1036.170522
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =   -1036.149761
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -22.89
 ---------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      42.21
 Dispersion energy                       (kcal/mol) =     -31.68
 Repulsion energy                        (kcal/mol) =       2.51
 Total non electrostatic                 (kcal/mol) =      13.03
 ---------------------------------------------------------------------
```

Iodobenzene

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6             0       -1.263891    1.215616   -0.000105
    2          6             0       -2.661405    1.207165    0.000040
    3          6             0       -3.361797   -0.000004   -0.000204
    4          6             0       -2.661393   -1.207171    0.000047
    5          6             0       -1.263885   -1.215612   -0.000118
    6          6             0       -0.581106    0.000009   -0.000078
    7         53             0        1.567003    0.000000    0.000008
    8          1             0       -0.722428    2.155325    0.000342
    9          1             0       -3.198684    2.151764    0.000572
   10          1             0       -4.448079   -0.000017    0.000255
   11          1             0       -3.198676   -2.151768    0.000583
   12          1             0       -0.722402   -2.155309    0.000352
 ---------------------------------------------------------------------
```

```
 Zero-point correction=                           0.090291
(Hartree/Particle)
 Thermal correction to Energy=                    0.096185
 Thermal correction to Enthalpy=                  0.097130
 Thermal correction to Gibbs Free Energy=         0.058517
 Sum of electronic and zero-point Energies=           -242.931203
 Sum of electronic and thermal Energies=              -242.925309
 Sum of electronic and thermal Enthalpies=            -242.924364
 Sum of electronic and thermal Free Energies=         -242.962977
-----------------------------------------------------------------

 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -243.021067
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -243.026633
 Total free energy in solution:
  with all non electrostatic te243.026633+rms            (a.u.) =    -
243.023994
 -----------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =      -3.49
 -----------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      15.15
 Dispersion energy                        (kcal/mol) =     -14.78
 Repulsion energy                         (kcal/mol) =       1.28
 Total non electrostatic                  (kcal/mol) =       1.66
 -----------------------------------------------------------------
```

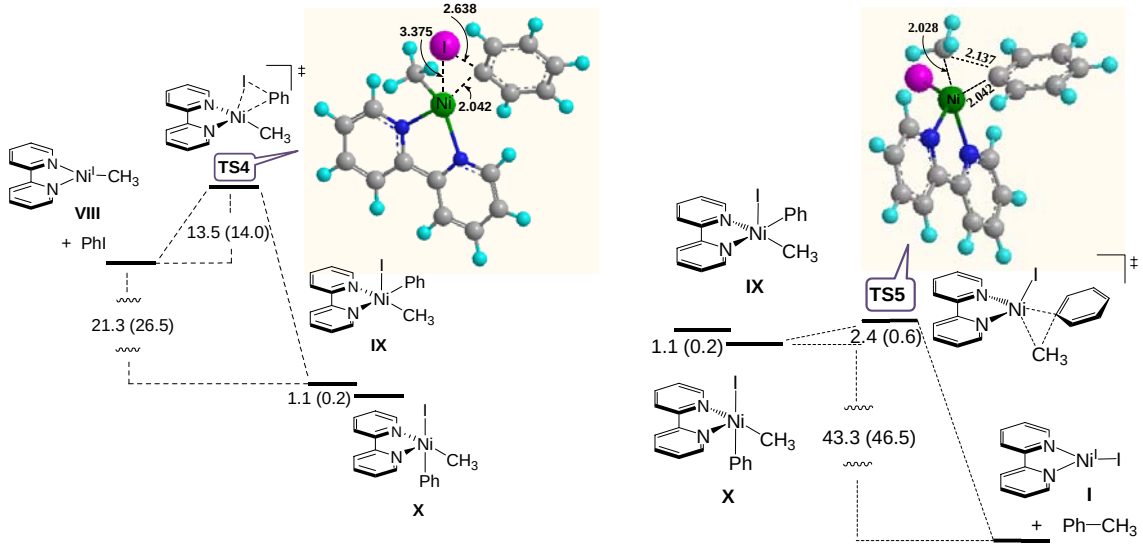
MeZnI

```
-----------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 -----------------------------------------------------------------------
    1          1             0        0.000000    1.026887   -3.653263
    2          6             0        0.000000    0.000000   -3.276277
    3          1             0       -0.889310   -0.513443   -3.653263
    4          1             0        0.889310   -0.513443   -3.653263
    5         30             0        0.000000    0.000000   -1.277898
    6         53             0        0.000000    0.000000    1.301026
 -----------------------------------------------------------------------

 Zero-point correction=                           0.036220
(Hartree/Particle)
 Thermal correction to Energy=                    0.041588
 Thermal correction to Enthalpy=                  0.042532
 Thermal correction to Gibbs Free Energy=         0.006562
 Sum of electronic and zero-point Energies=           -116.896881
 Sum of electronic and thermal Energies=              -116.891513
 Sum of electronic and thermal Enthalpies=            -116.890569
 Sum of electronic and thermal Free Energies=         -116.926539

-----------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -116.928884
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -116.944729
 Total free energy in solution:
```

```
 with all non electrostatic terms            (a.u.) =    -116.937062
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent                (kcal/mol) =      -9.94
 ---------------------------------------------------------------------
 Cavitation energy                         (kcal/mol) =      12.95
 Dispersion energy                         (kcal/mol) =      -8.91
 Repulsion energy                          (kcal/mol) =       0.77
 Total non electrostatic                   (kcal/mol) =       4.81
 ---------------------------------------------------------------------
```

ZnI_2

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         30             0        0.000000    0.000000    0.000000
    2         53             0        0.000000    0.000000    2.534536
    3         53             0        0.000000    0.000000   -2.534536
 ---------------------------------------------------------------------
 Zero-point correction=                           0.001239
(Hartree/Particle)
 Thermal correction to Energy=                    0.006339
 Thermal correction to Enthalpy=                  0.007283
 Thermal correction to Gibbs Free Energy=        -0.029291
 Sum of electronic and zero-point Energies=           -88.458242
 Sum of electronic and thermal Energies=              -88.453142
 Sum of electronic and thermal Enthalpies=            -88.452198
 Sum of electronic and thermal Free Energies=         -88.488772

  ---------------------------------------------------------------------
 Variational PCM results
 ======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =     -88.447755
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =     -88.495801
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =     -88.494301
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent                (kcal/mol) =     -30.15
 ---------------------------------------------------------------------
 Cavitation energy                         (kcal/mol) =      12.59
 Dispersion energy                         (kcal/mol) =     -13.11
 Repulsion energy                          (kcal/mol) =       1.46
 Total non electrostatic                   (kcal/mol) =       0.94
 ---------------------------------------------------------------------
```



B3LYP/6-31G(d) (C, H, N), LANL2DZ (Ni, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy differences in THF calculated with the PCM model are shown in brackets; Figures include the geometry of the **TS4** and **TS5**, in which specified distances are in Å.

VIII

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	1.726354	0.113382	0.000000
2	7	0	0.303182	-1.314457	0.000000
3	6	0	-1.783574	-3.176502	0.000000
4	6	0	-0.992411	-0.898297	0.000000
5	6	0	0.551763	-2.637720	0.000000
6	6	0	-0.451405	-3.599373	0.000000
7	6	0	-2.052932	-1.811177	0.000000
8	1	0	1.601103	-2.916760	0.000000
9	1	0	-0.192117	-4.653075	0.000000
10	1	0	-3.079198	-1.460572	0.000000
11	1	0	-2.596471	-3.896350	0.000000
12	7	0	0.000000	1.261531	0.000000
13	6	0	-2.425115	2.620136	0.000000
14	6	0	-0.029694	2.600535	0.000000
15	6	0	-1.162795	0.569668	0.000000
16	6	0	-2.398962	1.228191	0.000000
17	6	0	-1.219089	3.324749	0.000000
18	1	0	0.941254	3.086895	0.000000
19	1	0	-3.327194	0.667441	0.000000
20	1	0	-1.197791	4.409635	0.000000
21	1	0	-3.374650	3.147495	0.000000
22	6	0	3.493005	0.994143	0.000000
23	1	0	4.317866	0.264535	0.000000
24	1	0	3.637128	1.630212	0.887026
25	1	0	3.637128	1.630212	-0.887026

```
 Zero-point correction=                           0.194413
(Hartree/Particle)
 Thermal correction to Energy=                    0.207678
 Thermal correction to Enthalpy=                  0.208622
 Thermal correction to Gibbs Free Energy=         0.152070
 Sum of electronic and zero-point Energies=           -704.413419
 Sum of electronic and thermal Energies=              -704.400154
 Sum of electronic and thermal Enthalpies=            -704.399210
 Sum of electronic and thermal Free Energies=         -704.455762

-------------------------------------------------------------------
 Variational PCM results
 ======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -704.604150
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -704.623267
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -704.609247
 -------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -12.00
 -------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      24.93
 Dispersion energy                        (kcal/mol) =     -17.29
 Repulsion energy                         (kcal/mol) =       1.16
 Total non electrostatic                  (kcal/mol) =       8.80
 -------------------------------------------------------------------
```

TS4

```
-------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 -------------------------------------------------------------------
    1         28             0       -0.000223    0.257398    1.036485
    2          6             0       -0.604188   -0.522260    2.764397
    3          1             0       -1.336940   -1.317833    2.590921
    4          1             0       -1.065878    0.257840    3.384555
    5          1             0        0.258445   -0.935837    3.306720
    6          7             0        1.521635    1.527802    0.121211
    7          6             0        3.688066    2.988828   -0.834594
    8          6             0        1.451888    2.861723    0.004442
    9          6             0        2.662704    0.891664   -0.229093
   10          6             0        3.765766    1.604715   -0.719383
   11          6             0        2.509060    3.636649   -0.462174
   12          7             0        1.503539   -1.104563    0.422719
   13          6             0        3.664705   -2.769077   -0.105006
   14          6             0        1.411980   -2.424902    0.631957
   15          6             0        2.657587   -0.581559   -0.046412
   16          6             0        3.762818   -1.397282   -0.320649
   17          6             0        2.468664   -3.296551    0.381141
   18          1             0        4.535744    3.552938   -1.212401
   19          1             0        0.502057    3.309411    0.281780
   20          1             0        4.673592    1.089105   -1.009717
   21          1             0        2.405162    4.714043   -0.535944
   22          1             0        4.512234   -3.415340   -0.313875
   23          1             0        0.453117   -2.774684    0.996938
   24          1             0        4.687944   -0.973985   -0.694268
   25          1             0        2.348888   -4.359707    0.560420
   26         53             0       -1.925632   -1.761577   -0.862497
```

```
   27          6             0       -1.784460    0.676544    0.135795
   28          6             0       -3.276127    3.045978   -0.140315
   29          6             0       -2.836010    0.963293    1.027022
   30          6             0       -1.540804    1.553046   -0.940234
   31          6             0       -2.266693    2.743623   -1.056440
   32          6             0       -3.559912    2.147914    0.895564
   33          1             0       -3.853282    3.960972   -0.243810
   34          1             0       -3.070583    0.269019    1.825912
   35          1             0       -0.797480    1.298337   -1.688944
   36          1             0       -2.061028    3.416354   -1.886464
   37          1             0       -4.353755    2.369080    1.605298
 ---------------------------------------------------------------------

 Zero-point correction=                           0.285329
(Hartree/Particle)
 Thermal correction to Energy=                    0.305740
 Thermal correction to Enthalpy=                  0.306685
 Thermal correction to Gibbs Free Energy=         0.231482
 Sum of electronic and zero-point Energies=           -947.323129
 Sum of electronic and thermal Energies=              -947.302717
 Sum of electronic and thermal Enthalpies=            -947.301773
 Sum of electronic and thermal Free Energies=         -947.376976

---------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -947.600859
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =    -947.627597
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =    -947.610326
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -16.78
 ---------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      34.84
 Dispersion energy                       (kcal/mol) =     -25.88
 Repulsion energy                        (kcal/mol) =       1.89
 Total non electrostatic                 (kcal/mol) =      10.84
 ---------------------------------------------------------------------
```

IX

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0       -0.323360   -0.326558    0.718524
    2          7             0        0.172035    1.445836   -0.268272
    3          6             0        1.039069    3.669818   -1.687030
    4          6             0       -0.694915    2.181255   -0.974213
    5          6             0        1.479470    1.785867   -0.252320
    6          6             0        1.942600    2.902934   -0.955531
    7          6             0       -0.305050    3.304433   -1.700433
    8          7             0        1.750130   -0.155100    1.135049
    9          6             0        4.493937    0.196131    1.420104
   10          6             0        2.361946    0.892866    0.537910
   11          6             0        2.477321   -1.010816    1.861662
   12          6             0        3.852690   -0.877016    2.034890
   13          6             0        3.741293    1.091407    0.665012
   14         53             0        0.202387   -1.816745   -1.591998
   15          6             0       -2.214622   -0.033659    0.812282
```

```
  16          6             0       -4.894678    0.817439    0.873753
  17          6             0       -3.108347   -0.443243   -0.184219
  18          6             0       -2.680263    0.781153    1.854379
  19          6             0       -4.011678    1.212124    1.880789
  20          6             0       -4.439984   -0.011735   -0.154452
  21          6             0       -0.756999   -1.829654    1.866131
  22          1             0        1.384867    4.537514   -2.241065
  23          1             0       -1.724722    1.841730   -0.952212
  24          1             0        2.992214    3.171532   -0.942483
  25          1             0       -1.041666    3.869062   -2.261908
  26          1             0        5.565846    0.336426    1.523324
  27          1             0        1.932300   -1.833706    2.311616
  28          1             0        4.398412   -1.600289    2.631299
  29          1             0        4.227267    1.928875    0.178808
  30          1             0       -5.930782    1.145999    0.895256
  31          1             0       -2.764339   -1.091753   -0.984631
  32          1             0       -2.012876    1.089600    2.658251
  33          1             0       -4.356781    1.849812    2.691889
  34          1             0       -5.124168   -0.331726   -0.937376
  35          1             0       -0.743608   -1.446602    2.894489
  36          1             0        0.076760   -2.509087    1.668767
  37          1             0       -1.697036   -2.337225    1.663469
 ---------------------------------------------------------------------

 Zero-point correction=                           0.288583
(Hartree/Particle)
 Thermal correction to Energy=                    0.308866
 Thermal correction to Enthalpy=                  0.309810
 Thermal correction to Gibbs Free Energy=         0.235895
 Sum of electronic and zero-point Energies=           -947.378581
 Sum of electronic and thermal Energies=              -947.358298
 Sum of electronic and thermal Enthalpies=            -947.357354
 Sum of electronic and thermal Free Energies=         -947.431269

-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -947.660862
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -947.692156
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -947.675322
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -19.64
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      34.56
 Dispersion energy                        (kcal/mol) =     -25.89
 Repulsion energy                         (kcal/mol) =       1.89
 Total non electrostatic                  (kcal/mol) =      10.56
 ---------------------------------------------------------------------
```

X

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0        0.156396   -0.577874   -0.536382
    2          6             0        2.096627   -0.568934   -0.508559
    3          6             0        4.874420   -0.576886   -0.077654
    4          6             0        2.727515   -1.695854    0.031644
```

```
    5          6             0        2.869251    0.543447   -0.854556
    6          6             0        4.251118    0.541728   -0.635769
    7          6             0        4.109671   -1.696327    0.255224
    8          6             0        0.465708   -1.367320   -2.310140
    9          1             0        5.948717   -0.579210    0.087944
   10          1             0        2.150804   -2.586788    0.276476
   11          1             0        2.403228    1.421126   -1.296929
   12          1             0        4.841126    1.415559   -0.904625
   13          1             0        4.586979   -2.577283    0.678932
   14          1             0        1.201837   -0.820480   -2.901367
   15          1             0       -0.534590   -1.318826   -2.747231
   16          1             0        0.771504   -2.406309   -2.179091
   17          7             0        0.023894    0.333991    1.338053
   18          6             0       -0.238732    1.680680    3.751172
   19          6             0        0.270378   -0.290894    2.494177
   20          6             0       -0.356401    1.628487    1.345815
   21          6             0       -0.498207    2.331334    2.548459
   22          6             0        0.155248    0.343584    3.727921
   23          7             0       -0.395454    1.405555   -1.039925
   24          6             0       -1.286557    3.998167   -1.473520
   25          6             0       -0.613860    2.224268    0.012208
   26          6             0       -0.613282    1.849958   -2.282708
   27          6             0       -1.058640    3.142239   -2.550217
   28          6             0       -1.063366    3.536351   -0.179251
   29          1             0       -0.344754    2.211762    4.692402
   30          1             0        0.562409   -1.332716    2.417294
   31          1             0       -0.805936    3.370431    2.550572
   32          1             0        0.364973   -0.202726    4.641220
   33          1             0       -1.637653    5.012809   -1.636564
   34          1             0       -0.425015    1.137690   -3.078991
   35          1             0       -1.223756    3.460534   -3.573994
   36          1             0       -1.244098    4.189117    0.666616
   37         53             0       -2.168665   -1.889343   -0.085403
 ---------------------------------------------------------------------
Zero-point correction=                           0.288543
(Hartree/Particle)
 Thermal correction to Energy=                    0.308782
 Thermal correction to Enthalpy=                  0.309726
 Thermal correction to Gibbs Free Energy=         0.235780
 Sum of electronic and zero-point Energies=           -947.380356
 Sum of electronic and thermal Energies=              -947.360117
 Sum of electronic and thermal Enthalpies=            -947.359172
 Sum of electronic and thermal Free Energies=         -947.433119

-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -947.660745
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -947.692437
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -947.674845
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -19.89
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      34.87
 Dispersion energy                        (kcal/mol) =     -25.76
 Repulsion energy                         (kcal/mol) =       1.93
 Total non electrostatic                  (kcal/mol) =      11.04
 ---------------------------------------------------------------------
```

TS5

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.338745	0.077264	-0.568321
2	6	0	0.666060	1.974419	-0.377032
3	6	0	0.917496	4.436946	0.949550
4	6	0	1.868934	2.315319	0.258416
5	6	0	-0.391518	2.894836	-0.386291
6	6	0	-0.268800	4.113726	0.284957
7	6	0	1.984227	3.535766	0.931428
8	6	0	0.990716	1.001200	-2.252177
9	1	0	1.013785	5.389430	1.464017
10	1	0	2.707011	1.623724	0.232950
11	1	0	-1.314472	2.662862	-0.911901
12	1	0	-1.101063	4.814228	0.283979
13	1	0	2.916812	3.784482	1.432573
14	1	0	0.400860	1.775932	-2.742622
15	1	0	0.830691	0.028516	-2.741568
16	1	0	2.052151	1.235269	-2.280614
17	7	0	-0.527133	-0.484184	1.260420
18	6	0	-1.820775	-1.094804	3.640846
19	6	0	0.166400	-0.601432	2.398535
20	6	0	-1.862286	-0.677142	1.269945
21	6	0	-2.541712	-0.986496	2.454232
22	6	0	-0.440942	-0.900326	3.616652
23	7	0	-1.738849	-0.171084	-1.075534
24	6	0	-4.430253	-0.701993	-1.530600
25	6	0	-2.532628	-0.552069	-0.049747
26	6	0	-2.261278	-0.058422	-2.303135
27	6	0	-3.601894	-0.311878	-2.582000
28	6	0	-3.891535	-0.824253	-0.252830
29	1	0	-2.332099	-1.331821	4.569225
30	1	0	1.239415	-0.470024	2.307105
31	1	0	-3.614992	-1.137257	2.458006
32	1	0	0.159487	-0.983280	4.516326
33	1	0	-5.481482	-0.914352	-1.701580
34	1	0	-1.571963	0.245791	-3.084442
35	1	0	-3.977543	-0.208564	-3.594437
36	1	0	-4.521595	-1.138283	0.570906
37	53	0	2.333410	-1.779878	-0.426106

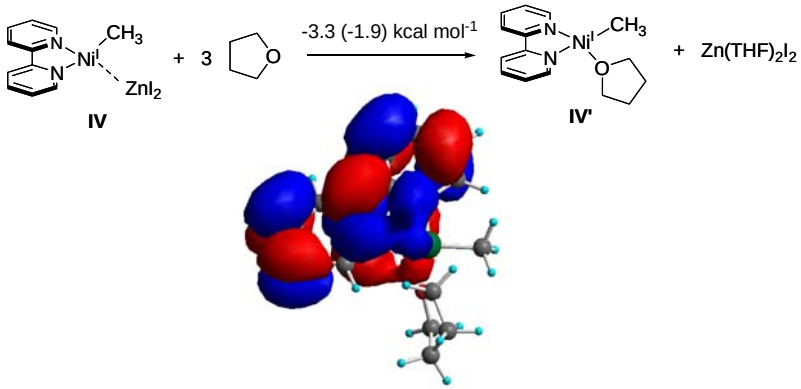
Zero-point correction= 0.287964
(Hartree/Particle)
Thermal correction to Energy= 0.307717
Thermal correction to Enthalpy= 0.308661
Thermal correction to Gibbs Free Energy= 0.235824
Sum of electronic and zero-point Energies= -947.376534
Sum of electronic and thermal Energies= -947.356780
Sum of electronic and thermal Enthalpies= -947.355836
Sum of electronic and thermal Free Energies= -947.428673

Variational PCM results
<psi(f)| H |psi(f)> (a.u.) = -947.658834
<psi(f)|H+V(f)/2|psi(f)> (a.u.) = -947.691424
Total free energy in solution:
with all non electrostatic terms (a.u.) = -947.674221

```
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -20.45
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      34.85
 Dispersion energy                        (kcal/mol) =     -25.98
 Repulsion energy                         (kcal/mol) =       1.92
 Total non electrostatic                  (kcal/mol) =      10.79
 ---------------------------------------------------------------------
```

Toluene

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6              0       -0.192306    1.203795   -0.006481
    2          6              0        1.204611    1.204107    0.001522
    3          6              0        1.905477   -0.002323    0.006162
    4          6              0        1.198335   -1.207391    0.001534
    5          6              0       -0.196501   -1.201670   -0.006501
    6          6              0       -0.913993    0.003593   -0.008004
    7          6              0       -2.425825    0.001592    0.006700
    8          1              0       -0.730435    2.149321   -0.013197
    9          1              0        1.743396    2.148317    0.001144
   10          1              0        2.992254   -0.005399    0.010215
   11          1              0        1.734366   -2.153207    0.001090
   12          1              0       -0.738795   -2.145091   -0.013052
   13          1              0       -2.833629   -0.741562   -0.688410
   14          1              0       -2.830593    0.980279   -0.271439
   15          1              0       -2.815349   -0.242871    1.004057
 ---------------------------------------------------------------------
Zero-point correction=                           0.128376
(Hartree/Particle)
 Thermal correction to Energy=                    0.134565
 Thermal correction to Enthalpy=                  0.135509
 Thermal correction to Gibbs Free Energy=         0.097873
 Sum of electronic and zero-point Energies=           -271.432710
 Sum of electronic and thermal Energies=              -271.426522
 Sum of electronic and thermal Enthalpies=            -271.425578
 Sum of electronic and thermal Free Energies=         -271.463213

 ---------------------------------------------------------------------
 Variational PCM results
 ======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -271.560820
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =    -271.564732
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =    -271.557874
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =      -2.45
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      14.83
 Dispersion energy                        (kcal/mol) =     -11.28
 Repulsion energy                         (kcal/mol) =       0.76
 Total non electrostatic                  (kcal/mol) =       4.30
 ---------------------------------------------------------------------
```



B3LYP/6-31G(d) (C, H, N, O), LANL2DZ (Ni, Zn, I); Δ(E+ZPE) is given in kcal mol^{-1}; Energy difference in THF calculated with the PCM model is shown in brackets.

IV'

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.336610	-0.693876	0.003345
2	8	0	2.235204	-0.117857	-0.014879
3	6	0	3.060351	-0.330281	-1.196721
4	6	0	4.482412	-0.560589	-0.670321
5	6	0	4.454424	0.101562	0.718759
6	6	0	3.036290	-0.209208	1.189898
7	1	0	2.973755	0.573178	-1.808879
8	1	0	2.656463	-1.180493	-1.749528
9	1	0	4.682993	-1.633146	-0.573253
10	1	0	5.240154	-0.133797	-1.333490
11	1	0	4.601132	1.184613	0.636383
12	1	0	5.213594	-0.296557	1.398057
13	1	0	2.623468	0.507839	1.903022
14	1	0	2.949173	-1.221386	1.600302
15	7	0	-0.262915	1.195310	-0.014598
16	6	0	-1.456272	3.729097	-0.037004
17	6	0	-1.645076	1.310866	-0.010358
18	6	0	0.484184	2.315683	-0.031806
19	6	0	-0.042605	3.592977	-0.042954
20	6	0	-2.242010	2.600833	-0.021318
21	7	0	-1.534164	-1.071896	0.010683
22	6	0	-4.337723	-1.312397	0.017311
23	6	0	-2.137186	-2.282781	0.020253
24	6	0	-2.340533	0.070966	0.003134
25	6	0	-3.753096	-0.069261	0.007426
26	6	0	-3.504421	-2.461730	0.023618
27	1	0	-1.914229	4.714431	-0.045537
28	1	0	1.558052	2.152529	-0.037748
29	1	0	0.612501	4.457381	-0.056673
30	1	0	-3.323415	2.691060	-0.017614
31	1	0	-5.419470	-1.412169	0.019871
32	1	0	-1.474656	-3.138120	0.025250
33	1	0	-4.369911	0.823465	0.001948
34	1	0	-3.916562	-3.464856	0.030951
35	6	0	0.878740	-2.552490	0.025094
36	1	0	0.487017	-3.050642	0.921438

```
   37          1             0        1.972369   -2.655490    0.032566
   38          1             0        0.495528   -3.069852   -0.864367
 ---------------------------------------------------------------------

 Zero-point correction=                           0.315417
(Hartree/Particle)
 Thermal correction to Energy=                    0.333742
 Thermal correction to Enthalpy=                  0.334686
 Thermal correction to Gibbs Free Energy=         0.267421
 Sum of electronic and zero-point Energies=           -936.741830
 Sum of electronic and thermal Energies=              -936.723506
 Sum of electronic and thermal Enthalpies=            -936.722561
 Sum of electronic and thermal Free Energies=         -936.789827

---------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -937.055531
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -937.067545
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -937.051717
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =      -7.54
 ---------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      31.14
 Dispersion energy                       (kcal/mol) =     -22.54
 Repulsion energy                        (kcal/mol) =       1.33
 Total non electrostatic                 (kcal/mol) =       9.93
 ---------------------------------------------------------------------
```

THF

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          8             0        0.000000    0.000000    1.251036
    2          6             0        0.000000    1.172465    0.431074
    3          6             0       -0.308283    0.703581   -0.996839
    4          6             0        0.308283   -0.703581   -0.996839
    5          6             0        0.000000   -1.172465    0.431074
    6          1             0        0.987818    1.656471    0.483085
    7          1             0       -0.742517    1.877093    0.823940
    8          1             0       -1.391901    0.643743   -1.155061
    9          1             0        0.110355    1.365339   -1.761520
   10          1             0        1.391901   -0.643743   -1.155061
   11          1             0       -0.110355   -1.365339   -1.761520
   12          1             0        0.742517   -1.877093    0.823940
   13          1             0       -0.987818   -1.656471    0.483085
 ---------------------------------------------------------------------

 Zero-point  correction=                                  0.117460
(Hartree/Particle)
 Thermal correction to Energy=                    0.122400
 Thermal correction to Enthalpy=                  0.123344
 Thermal correction to Gibbs Free Energy=         0.089587
 Sum of electronic and zero-point Energies=           -232.328196
 Sum of electronic and thermal Energies=              -232.323257
 Sum of electronic and thermal Enthalpies=            -232.322313
```

```
 Sum of electronic and thermal Free Energies=         -232.356070

-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -232.445192
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -232.449143
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -232.444374
 -------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =      -2.48
 -------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      11.90
 Dispersion energy                        (kcal/mol) =      -9.42
 Repulsion energy                         (kcal/mol) =       0.51
 Total non electrostatic                  (kcal/mol) =       2.99
 -------------------------------------------------------------------
```

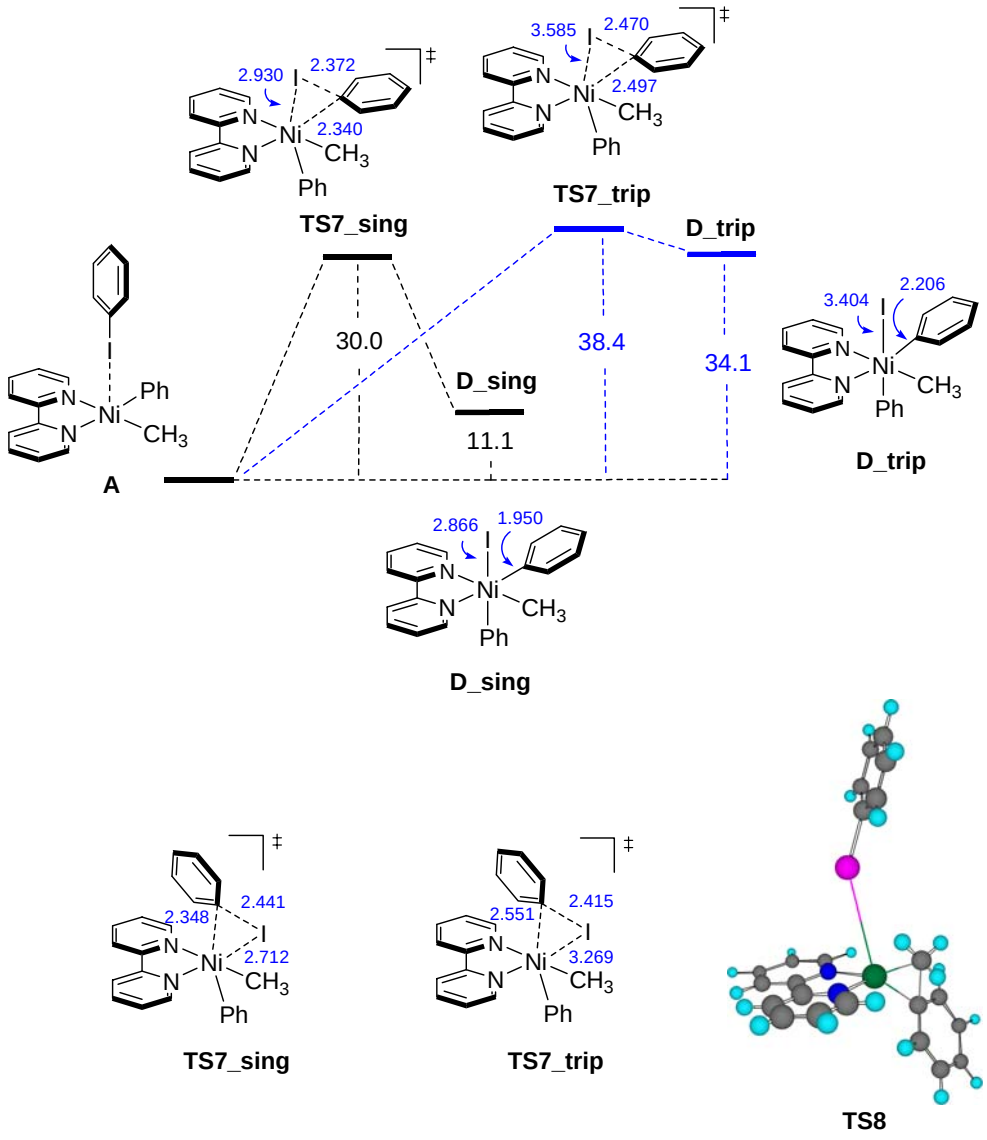
$ZnI_2(THF)_2$

```
-------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 -------------------------------------------------------------------
    1         30             0       -0.039205    0.004240   -0.178434
    2         53             0        1.943650   -1.268788   -1.393894
    3         53             0       -2.192362    1.235373   -1.102558
    4          8             0       -0.663496   -1.248786    1.439505
    5          6             0       -0.159482   -2.578790    1.721108
    6          6             0       -1.404830   -3.458970    1.657602
    7          6             0       -2.524268   -2.543008    2.214820
    8          6             0       -1.943017   -1.114634    2.119788
    9          1             0        0.292357   -2.573276    2.722406
   10          1             0        0.604629   -2.800530    0.975062
   11          1             0       -1.610958   -3.730803    0.617895
   12          1             0       -1.286698   -4.381855    2.232559
   13          1             0       -2.763903   -2.789862    3.253485
   14          1             0       -3.442991   -2.638691    1.630682
   15          1             0       -1.756052   -0.677417    3.107400
   16          1             0       -2.543759   -0.424439    1.526178
   17          8             0        0.919603    1.441476    1.074689
   18          6             0        2.009244    1.083599    1.957492
   19          6             0        2.301312    2.380623    2.711335
   20          6             0        1.992235    3.488208    1.668701
   21          6             0        1.218266    2.764767    0.546912
   22          1             0        2.862808    0.742255    1.358790
   23          1             0        1.655217    0.262264    2.583278
   24          1             0        1.636546    2.470550    3.575694
   25          1             0        3.332742    2.416310    3.072986
   26          1             0        2.907603    3.936074    1.271958
   27          1             0        1.396840    4.290766    2.111467
   28          1             0        1.825363    2.651105   -0.358698
   29          1             0        0.262524    3.219026    0.283731
 -------------------------------------------------------------------
 Zero-point correction=                   0.240067 (Hartree/Particle)
 Thermal correction to Energy=                0.256351
 Thermal correction to Enthalpy=              0.257295
 Thermal correction to Gibbs Free Energy=     0.188754
 Sum of electronic and zero-point Energies=          -553.175952
```

```
 Sum of electronic and thermal Energies=              -553.159668
 Sum of electronic and thermal Enthalpies=            -553.158723
 Sum of electronic and thermal Free Energies=         -553.227265
-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =    -553.413630
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =    -553.431714
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =    -553.416329
 -------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -11.35
 -------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      30.90
 Dispersion energy                        (kcal/mol) =     -22.79
 Repulsion energy                         (kcal/mol) =       1.55
 Total non electrostatic                  (kcal/mol) =       9.65
 -------------------------------------------------------------------
```

III. Computational study of the oxidative addition of PhI to (bpy)Ni(Me)Ph

Triplet transition states correspond to the oxidative addition of radical anion of PhI, which would be formed by electron transfer from **A** to PhI. We also calculated singlet and triplet transition states with different geometry, which will be called **TS6** and **TS7**. **TS7_sing** is 3.8 kcal mol^{-1} less stable than **TS6_sing**, whereas **TS7_trip** is 3.4 kcal mol^{-1} more stable than **TS6_trip**. Reductive elimination from complex **B** associated to **C** the radical anion of PhI **(**see main text) through **TS8** shows a high activation energy (27 kcal mol^{-1}).



Energy profile for the oxidative addition of PhI to Ni^{II} complex **A**. B3LYP/6-31G(d) (C, H, N), LANL2DZ (Ni, I); Δ(E+ZPE) (kcal mol^{-1}). The specified distances included in the figures are given in Å.

A

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	1.928059	0.082711	-0.818442
2	6	0	2.638730	-1.660951	-0.629055
3	6	0	3.789384	-4.211132	-0.104551
4	6	0	4.035044	-1.849615	-0.598498
5	6	0	1.839439	-2.798994	-0.405166
6	6	0	2.401969	-4.053176	-0.140853
7	6	0	4.604757	-3.101484	-0.338454
8	1	0	4.699240	-1.005808	-0.782157
9	1	0	0.754705	-2.713324	-0.439580
10	1	0	1.753210	-4.910603	0.031267
11	1	0	5.688134	-3.210061	-0.322240
12	1	0	4.228684	-5.185786	0.095701
13	6	0	1.750892	-0.277507	-2.700462
14	1	0	0.724146	-0.001716	-2.988471
15	1	0	1.934383	-1.300759	-3.032162
16	1	0	2.461466	0.385061	-3.220295
17	7	0	2.008676	0.561370	1.146675
18	6	0	1.956991	1.417418	3.801780
19	6	0	2.365260	-0.265290	2.142496
20	6	0	1.622590	1.824350	1.451797
21	6	0	1.585650	2.279820	2.773585
22	6	0	2.355262	0.121017	3.480915
23	1	0	2.663869	-1.260949	1.835453
24	1	0	1.267635	3.290793	3.001267
25	1	0	2.653327	-0.586443	4.247737
26	1	0	1.933070	1.754498	4.833948
27	7	0	1.300926	2.005889	-0.907335
28	6	0	0.557513	4.695186	-0.788058
29	6	0	0.986667	2.685763	-2.020104
30	6	0	1.252262	2.652284	0.284532
31	6	0	0.883414	3.998854	0.372103
32	6	0	0.610540	4.026379	-2.009652
33	1	0	1.041807	2.122200	-2.944046
34	1	0	0.853720	4.500711	1.332330
35	1	0	0.366418	4.526061	-2.941295
36	1	0	0.269566	5.741060	-0.736509
37	53	0	-1.898280	-0.435249	-0.368525
38	6	0	-3.985699	-0.642084	0.076253
39	6	0	-6.698402	-0.919168	0.650931
40	6	0	-4.378203	-1.168338	1.307376
41	6	0	-4.933146	-0.253998	-0.871647
42	6	0	-6.291872	-0.395356	-0.577281
43	6	0	-5.740001	-1.304588	1.589568
44	1	0	-3.636353	-1.472004	2.038421
45	1	0	-4.621390	0.150823	-1.828697
46	1	0	-7.030901	-0.094783	-1.315371
47	1	0	-6.047062	-1.715747	2.547679
48	1	0	-7.755948	-1.028113	0.874551

Zero-point correction= 0.378093
(Hartree/Particle)
Thermal correction to Energy= 0.404330
Thermal correction to Enthalpy= 0.405274
Thermal correction to Gibbs Free Energy= 0.310483
Sum of electronic and zero-point Energies= -1178.896089

```
 Sum of electronic and thermal Energies=             -1178.869853
 Sum of electronic and thermal Enthalpies=           -1178.868909
 Sum of electronic and thermal Free Energies=        -1178.963699

-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.269745
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =   -1179.293427
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =   -1179.267967
 -------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -14.86
 -------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      46.04
 Dispersion energy                       (kcal/mol) =     -32.44
 Repulsion energy                        (kcal/mol) =       2.37
 Total non electrostatic                 (kcal/mol) =      15.98
 -------------------------------------------------------------------
```

TS6_sing

singlet

-192 cm^{-1}

```
-------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 -------------------------------------------------------------------
    1         28             0        0.129607    0.133485   -0.650579
    2          6             0        1.271570    1.629427   -0.997297
    3          6             0        2.770354    4.007810   -1.318036
    4          6             0        0.670334    2.808091   -1.469680
    5          6             0        2.642610    1.661129   -0.709448
    6          6             0        3.383849    2.840259   -0.861605
    7          6             0        1.407471    3.986457   -1.625140
    8          6             0        0.499561   -0.286579   -2.500851
    9          1             0        3.347218    4.921448   -1.440665
   10          1             0       -0.388891    2.813797   -1.723605
   11          1             0        3.148467    0.763612   -0.366939
   12          1             0        4.447290    2.840408   -0.628743
   13          1             0        0.916649    4.886958   -1.990252
   14          1             0        0.092020   -1.297655   -2.641604
   15          1             0        1.553497   -0.267105   -2.781826
   16          1             0       -0.046289    0.429552   -3.125794
   17          7             0       -0.565597    1.032508    1.133244
   18          6             0       -1.537144    2.441665    3.338606
   19          6             0        0.269088    1.558085    2.042434
   20          6             0       -1.896646    1.230833    1.280703
   21          6             0       -2.408064    1.931000    2.382462
   22          6             0       -0.166625    2.260268    3.162338
   23          7             0       -2.117534    0.258661   -0.897310
   24          6             0       -4.898051    0.284891   -0.845161
   25          6             0       -2.824334   -0.177607   -1.943920
   26          6             0       -2.765669    0.725570    0.187312
   27          6             0       -4.166327    0.742412    0.247353
   28          6             0       -4.217780   -0.179339   -1.970313
   29          1             0       -1.922866    2.986293    4.195491
   30          1             0        1.325106    1.414295    1.844578
   31          1             0       -3.474496    2.094114    2.483121
   32          1             0        0.556112    2.660367    3.865694
```

33	1	0	-5.983794	0.288729	-0.814506
34	1	0	-2.242788	-0.545301	-2.784207
35	1	0	-4.683317	1.094997	1.132390
36	1	0	-4.748174	-0.544218	-2.843973
37	53	0	-0.519315	-2.599643	0.182250
38	6	0	1.574412	-1.485518	0.223979
39	6	0	4.295051	-1.597948	0.909734
40	6	0	2.517519	-1.932989	-0.713739
41	6	0	1.986256	-1.182342	1.530570
42	6	0	3.344808	-1.212832	1.856941
43	6	0	3.869474	-1.963002	-0.371937
44	1	0	5.348648	-1.636857	1.170989
45	1	0	2.203245	-2.245439	-1.701887
46	1	0	1.252775	-0.947846	2.292763
47	1	0	3.652110	-0.957899	2.868746
48	1	0	4.593806	-2.285396	-1.116179

```
 Zero-point correction=                           0.377639
(Hartree/Particle)
 Thermal correction to Energy=                    0.402779
 Thermal correction to Enthalpy=                  0.403724
 Thermal correction to Gibbs Free Energy=         0.320301
 Sum of electronic and zero-point Energies=          -1178.848330
 Sum of electronic and thermal Energies=             -1178.823189
 Sum of electronic and thermal Enthalpies=           -1178.822245
 Sum of electronic and thermal Free Energies=        -1178.905668

-----------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.223099
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1179.242528
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -1179.222845
 -----------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -12.19
 -----------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      40.18
 Dispersion energy                        (kcal/mol) =     -30.01
 Repulsion energy                         (kcal/mol) =       2.18
 Total non electrostatic                  (kcal/mol) =      12.35
 -----------------------------------------------------------------
```

TS6_trip

triplet

-245 cm^{-1}

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.475356	-0.155324	-0.608690
2	6	0	2.393586	-0.403868	-0.916785
3	6	0	5.170530	-0.829925	-1.088418
4	6	0	3.255408	0.650124	-1.237941
5	6	0	2.932884	-1.679408	-0.704645
6	6	0	4.315470	-1.889676	-0.780934
7	6	0	4.636475	0.439947	-1.320448

```
    8          6             0        0.277329   -0.670069   -2.494589
    9          1             0        6.243357   -0.993251   -1.154139
   10          1             0        2.859288    1.646837   -1.422428
   11          1             0        2.281829   -2.524540   -0.483950
   12          1             0        4.720353   -2.885028   -0.608977
   13          1             0        5.295673    1.270358   -1.566163
   14          1             0       -0.799308   -0.546257   -2.666428
   15          1             0        0.584649   -1.704610   -2.649651
   16          1             0        0.862899   -0.008469   -3.137395
   17          7             0        0.788993    0.546826    1.320710
   18          6             0        1.418632    1.744132    3.759146
   19          6             0        1.355080   -0.162512    2.310656
   20          6             0        0.551527    1.869675    1.511459
   21          6             0        0.858600    2.491245    2.729506
   22          6             0        1.678049    0.387237    3.545097
   23          7             0        0.009256    1.896681   -0.815017
   24          6             0       -0.951408    4.508060   -0.755758
   25          6             0       -0.443732    2.484610   -1.930978
   26          6             0        0.002468    2.590642    0.349257
   27          6             0       -0.486723    3.902993    0.405996
   28          6             0       -0.922226    3.789698   -1.954332
   29          1             0        1.663085    2.214480    4.706822
   30          1             0        1.547619   -1.206825    2.091493
   31          1             0        0.678394    3.551631    2.864060
   32          1             0        2.126928   -0.232758    4.313903
   33          1             0       -1.336725    5.522945   -0.726560
   34          1             0       -0.423583    1.875492   -2.827562
   35          1             0       -0.518581    4.438076    1.348144
   36          1             0       -1.275053    4.222639   -2.884255
   37         53             0       -3.081855   -0.207037   -0.163969
   38          6             0       -1.240239   -1.834706    0.077143
   39          6             0       -0.507009   -4.460258    0.780121
   40          6             0       -1.239856   -2.857791   -0.888168
   41          6             0       -0.971802   -2.166541    1.417776
   42          6             0       -0.582775   -3.464701    1.758202
   43          6             0       -0.846102   -4.150460   -0.542083
   44          1             0       -0.217360   -5.472442    1.048764
   45          1             0       -1.531217   -2.642257   -1.910869
   46          1             0       -1.073248   -1.416134    2.194950
   47          1             0       -0.357586   -3.700812    2.796360
   48          1             0       -0.815838   -4.922253   -1.307969
 ---------------------------------------------------------------------

 Zero-point correction=                           0.376252
(Hartree/Particle)
 Thermal correction to Energy=                    0.401843
 Thermal correction to Enthalpy=                  0.402787
 Thermal correction to Gibbs Free Energy=         0.315457
 Sum of electronic and zero-point Energies=          -1178.834918
 Sum of electronic and thermal Energies=             -1178.809327
 Sum of electronic and thermal Enthalpies=           -1178.808383
 Sum of electronic and thermal Free Energies=        -1178.895713

---------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.204810
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1179.231527
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -1179.208484
 ---------------------------------------------------------------------
```

(Polarized solute)-Solvent	(kcal/mol) =	-16.77
Cavitation energy	(kcal/mol) =	42.33
Dispersion energy	(kcal/mol) =	-30.09
Repulsion energy	(kcal/mol) =	2.22
Total non electrostatic	(kcal/mol) =	14.46

TS7_sing

singlet

-180 cm^{-1}

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.305646	-0.219944	-0.579376
2	6	0	2.213922	0.150495	-0.820280
3	6	0	4.965269	0.813812	-0.933829
4	6	0	2.638293	1.425964	-1.224718
5	6	0	3.199334	-0.790234	-0.494344
6	6	0	4.560202	-0.464012	-0.544817
7	6	0	3.995950	1.759205	-1.277210
8	6	0	0.491941	-0.726967	-2.451602
9	7	0	0.448542	0.716342	1.275973
10	6	0	0.684890	2.186429	3.628291
11	6	0	1.123510	0.226936	2.324488
12	6	0	-0.106837	1.946503	1.362787
13	6	0	-0.003696	2.705164	2.536554
14	6	0	1.264588	0.922416	3.522237
15	7	0	-0.818785	1.557528	-0.892269
16	6	0	-2.009461	4.057415	-1.155555
17	6	0	-1.419696	1.910725	-2.033600
18	6	0	-0.797736	2.426527	0.142278
19	6	0	-1.385529	3.694048	0.034095
20	6	0	-2.032234	3.148508	-2.213134
21	1	0	6.021741	1.067844	-0.977174
22	1	0	1.906294	2.179763	-1.511802
23	1	0	2.911933	-1.799064	-0.202332
24	1	0	5.304431	-1.215559	-0.286492
25	1	0	4.296032	2.757489	-1.591689
26	1	0	-0.513800	-1.029532	-2.767530
27	1	0	1.187298	-1.554000	-2.600895
28	1	0	0.820727	0.134462	-3.039462
29	1	0	0.770960	2.763174	4.544523
30	1	0	1.564601	-0.753621	2.182516
31	1	0	-0.455402	3.688173	2.600218
32	1	0	1.820016	0.481131	4.343102
33	1	0	-2.469862	5.036169	-1.253573
34	1	0	-1.405551	1.166439	-2.823012
35	1	0	-1.356346	4.392141	0.862776
36	1	0	-2.512602	3.387033	-3.156479
37	53	0	0.051242	-2.781939	0.272517
38	6	0	-1.763334	-1.173512	-0.010452
39	6	0	-4.492958	-0.532059	0.103985
40	6	0	-2.326431	-0.701569	1.183054
41	6	0	-2.586844	-1.404250	-1.118602
42	6	0	-3.941357	-1.063368	-1.063497
43	6	0	-3.680028	-0.363816	1.228791

44	1	0	-5.548564	-0.278073	0.146747
45	1	0	-1.718732	-0.600229	2.075534
46	1	0	-2.186438	-1.856226	-2.018962
47	1	0	-4.567567	-1.230771	-1.937139
48	1	0	-4.101917	0.021226	2.154783

Zero-point correction= 0.377587
(Hartree/Particle)
Thermal correction to Energy= 0.402646
Thermal correction to Enthalpy= 0.403590
Thermal correction to Gibbs Free Energy= 0.320734
Sum of electronic and zero-point Energies= -1178.842278
Sum of electronic and thermal Energies= -1178.817219
Sum of electronic and thermal Enthalpies= -1178.816275
Sum of electronic and thermal Free Energies= -1178.899131

Variational PCM results
<psi(f)| H |psi(f)> (a.u.) = -1179.216340
<psi(f)|H+V(f)/2|psi(f)> (a.u.) = -1179.237443
Total free energy in solution:
with all non electrostatic terms (a.u.) = -1179.217345

(Polarized solute)-Solvent	(kcal/mol) =	-13.24
Cavitation energy	(kcal/mol) =	40.09
Dispersion energy	(kcal/mol) =	-29.65
Repulsion energy	(kcal/mol) =	2.17
Total non electrostatic	(kcal/mol) =	12.61

TS7_trip

triplet

-252 cm^{-1}

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.386946	-0.049370	-0.659170
2	6	0	2.333014	-0.137928	-0.888076
3	6	0	5.142037	-0.278157	-1.025222
4	6	0	3.091876	1.011833	-1.136308
5	6	0	2.992939	-1.362523	-0.729184
6	6	0	4.390418	-1.430456	-0.789414
7	6	0	4.488082	0.943459	-1.200977
8	6	0	0.296899	-0.575518	-2.561020
9	7	0	0.568672	0.558088	1.327009
10	6	0	0.992690	1.650194	3.856928
11	6	0	1.095040	-0.181847	2.315293
12	6	0	0.258834	1.859007	1.567980
13	6	0	0.470202	2.429417	2.832527
14	6	0	1.313129	0.313812	3.595522
15	7	0	-0.162849	1.979961	-0.780861
16	6	0	-1.246979	4.539958	-0.647714
17	6	0	-0.576751	2.606080	-1.892082
18	6	0	-0.266401	2.610924	0.416577

```
   19          6             0       -0.821820    3.896682    0.507535
   20          6             0       -1.115240    3.887262   -1.879078
   21          1             0        6.226669   -0.331908   -1.077709
   22          1             0        2.603119    1.972938   -1.280480
   23          1             0        2.425440   -2.275497   -0.560456
   24          1             0        4.888417   -2.389283   -0.659082
   25          1             0        5.064191    1.847337   -1.390164
   26          1             0       -0.698434   -0.267788   -2.898430
   27          1             0        0.396184   -1.663599   -2.607856
   28          1             0        1.072700   -0.105976   -3.168315
   29          1             0        1.161240    2.079822    4.839990
   30          1             0        1.338269   -1.206374    2.057339
   31          1             0        0.245290    3.475777    3.005780
   32          1             0        1.728623   -0.331134    4.362356
   33          1             0       -1.678998    5.534789   -0.591417
   34          1             0       -0.463787    2.047314   -2.815118
   35          1             0       -0.930055    4.381237    1.471410
   36          1             0       -1.428182    4.356103   -2.805933
   37         53             0       -0.756559   -2.935256    0.366656
   38          6             0       -1.966496   -0.929111   -0.218968
   39          6             0       -4.366434    0.492285   -0.506846
   40          6             0       -2.489046   -0.202462    0.863995
   41          6             0       -2.703040   -1.025102   -1.410720
   42          6             0       -3.880811   -0.293222   -1.558590
   43          6             0       -3.669987    0.525375    0.704757
   44          1             0       -5.292541    1.048830   -0.621650
   45          1             0       -1.977726   -0.197534    1.820315
   46          1             0       -2.351042   -1.653250   -2.222495
   47          1             0       -4.428128   -0.347837   -2.497084
   48          1             0       -4.051793    1.110827    1.538471
 ---------------------------------------------------------------------

 Zero-point correction=                           0.375929
(Hartree/Particle)
 Thermal correction to Energy=                    0.401650
 Thermal correction to Enthalpy=                  0.402594
 Thermal correction to Gibbs Free Energy=         0.315631
 Sum of electronic and zero-point Energies=          -1178.840304
 Sum of electronic and thermal Energies=             -1178.814583
 Sum of electronic and thermal Enthalpies=           -1178.813639
 Sum of electronic and thermal Free Energies=        -1178.900602

---------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.210637
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1179.234293
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -1179.211990
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =     -14.84
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      41.66
 Dispersion energy                        (kcal/mol) =     -29.88
 Repulsion energy                         (kcal/mol) =       2.21
 Total non electrostatic                  (kcal/mol) =      14.00
 ---------------------------------------------------------------------
```

D_sing

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	-0.103419	-0.126736	0.589090
2	7	0	-0.059992	1.948770	0.268167
3	6	0	0.025394	4.660678	-0.363357
4	6	0	-0.090699	2.879245	1.228604
5	6	0	0.022631	2.340727	-1.023916
6	6	0	0.058472	3.697658	-1.366458
7	6	0	-0.046961	4.245089	0.963733
8	1	0	-0.143647	2.514024	2.246353
9	1	0	0.114644	4.002413	-2.404377
10	1	0	-0.070554	4.955516	1.783133
11	1	0	0.057781	5.716048	-0.616890
12	7	0	-0.029540	-0.003264	-1.538933
13	6	0	0.379330	0.406625	-4.263766
14	6	0	0.088331	1.253199	-2.025860
15	6	0	0.065494	-1.038715	-2.381007
16	6	0	0.265662	-0.882379	-3.750739
17	6	0	0.290482	1.486555	-3.390705
18	1	0	-0.015033	-2.021298	-1.932036
19	1	0	0.338179	-1.757240	-4.388075
20	1	0	0.397277	2.495797	-3.769480
21	1	0	0.544116	0.573368	-5.324118
22	6	0	-2.076416	-0.091002	0.805205
23	6	0	-4.892061	0.033078	0.964826
24	6	0	-2.762128	-0.707807	1.857552
25	6	0	-2.819473	0.581525	-0.170483
26	6	0	-4.217219	0.642841	-0.090969
27	6	0	-4.156390	-0.644163	1.938409
28	1	0	-2.224583	-1.259652	2.620185
29	1	0	-2.337874	1.065351	-1.012084
30	1	0	-4.771059	1.172984	-0.862961
31	1	0	-4.664496	-1.134031	2.765969
32	1	0	-5.976044	0.081939	1.027117
33	6	0	-0.138831	-2.072613	0.714554
34	6	0	-0.062962	-4.895282	0.686265
35	6	0	-1.142250	-2.811815	0.070785
36	6	0	0.892047	-2.767026	1.361265
37	6	0	0.928223	-4.165207	1.343422
38	6	0	-1.096725	-4.212252	0.048278
39	1	0	-1.971016	-2.313587	-0.419250
40	1	0	1.689107	-2.229525	1.860369
41	1	0	1.745813	-4.679233	1.843535
42	1	0	-1.885797	-4.760934	-0.461476
43	1	0	-0.032001	-5.981852	0.676513
44	6	0	0.044084	-0.013280	2.541713
45	1	0	1.047817	0.381552	2.687938
46	1	0	-0.070698	-0.992868	2.997859
47	1	0	-0.736406	0.663078	2.888707
48	53	0	2.738466	0.111022	0.302072

Zero-point correction= 0.381338
(Hartree/Particle)
Thermal correction to Energy= 0.406186
Thermal correction to Enthalpy= 0.407130
Thermal correction to Gibbs Free Energy= 0.325608
Sum of electronic and zero-point Energies= -1178.878321

```
 Sum of electronic and thermal Energies=             -1178.853472
 Sum of electronic and thermal Enthalpies=           -1178.852528
 Sum of electronic and thermal Free Energies=        -1178.934050

-------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.254213
 <psi(f)|H+V(f)/2|psi(f)>                   (a.u.) =   -1179.283928
 Total free energy in solution:
  with all non electrostatic terms          (a.u.) =   -1179.264544
 -------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -18.65
 -------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      39.89
 Dispersion energy                       (kcal/mol) =     -29.89
 Repulsion energy                        (kcal/mol) =       2.17
 Total non electrostatic                 (kcal/mol) =      12.16
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```

D_trip

```
-------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 -------------------------------------------------------------------
    1         28             0        0.255660   -0.335144   -0.589194
    2          6             0        1.989440   -1.081678   -1.080114
    3          6             0        4.528212   -2.264826   -1.320465
    4          6             0        3.101594   -0.306218   -1.421142
    5          6             0        2.150502   -2.459207   -0.890263
    6          6             0        3.416759   -3.046628   -1.000061
    7          6             0        4.366397   -0.893822   -1.534495
    8          6             0       -0.000718   -0.619768   -2.517879
    9          1             0        5.510554   -2.721071   -1.412784
   10          1             0        2.993094    0.761457   -1.597829
   11          1             0        1.289328   -3.083498   -0.659528
   12          1             0        3.529184   -4.117639   -0.845095
   13          1             0        5.225879   -0.278426   -1.792694
   14          1             0       -1.016413   -0.217026   -2.596985
   15          1             0        0.041416   -1.670285   -2.798489
   16          1             0        0.713754   -0.043859   -3.107887
   17          7             0        0.986102    0.140741    1.339349
   18          6             0        2.164980    0.890549    3.745818
   19          6             0        1.309970   -0.777269    2.259005
   20          6             0        1.263076    1.440947    1.578566
   21          6             0        1.852646    1.845338    2.782860
   22          6             0        1.895821   -0.450434    3.479223
   23          7             0        0.590568    1.814122   -0.690513
   24          6             0        0.697470    4.583260   -0.471260
   25          6             0        0.295338    2.593278   -1.736114
   26          6             0        0.943206    2.384423    0.479717
   27          6             0        0.997341    3.775887    0.622388
   28          6             0        0.345585    3.984115   -1.678812
   29          1             0        2.622826    1.190379    4.683842
   30          1             0        1.085296   -1.805353    1.998393
   31          1             0        2.081561    2.889277    2.961300
   32          1             0        2.135428   -1.231611    4.192770
   33          1             0        0.730601    5.664598   -0.376440
   34          1             0       -0.003517    2.079123   -2.642482
   35          1             0        1.252869    4.226619    1.574180
```

36	1	0	0.096682	4.573696	-2.554674
37	53	0	-2.869370	0.956401	-0.201478
38	6	0	-1.436873	-1.600815	0.041562
39	6	0	-2.465410	-4.095898	0.881458
40	6	0	-1.924151	-2.536844	-0.891353
41	6	0	-1.588467	-1.903252	1.410517
42	6	0	-2.067510	-3.146523	1.828095
43	6	0	-2.401182	-3.783535	-0.479622
44	1	0	-2.852727	-5.059512	1.203140
45	1	0	-1.924150	-2.302688	-1.951087
46	1	0	-1.340465	-1.158096	2.160635
47	1	0	-2.155659	-3.366293	2.890205
48	1	0	-2.738252	-4.505508	-1.220352

```
 Zero-point correction=                           0.377925
(Hartree/Particle)
 Thermal correction to Energy=                    0.404021
 Thermal correction to Enthalpy=                  0.404965
 Thermal correction to Gibbs Free Energy=         0.316942
 Sum of electronic and zero-point Energies=          -1178.841706
 Sum of electronic and thermal Energies=             -1178.815610
 Sum of electronic and thermal Enthalpies=           -1178.814666
 Sum of electronic and thermal Free Energies=        -1178.902689

 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.212656
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1179.242718
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -1179.220648
 (Polarized solute)-Solvent               (kcal/mol) =     -18.86
 Cavitation energy                        (kcal/mol) =      41.75
 Dispersion energy                        (kcal/mol) =     -30.12
 Repulsion energy                         (kcal/mol) =       2.22
 Total non electrostatic                  (kcal/mol) =      13.85
```

TS8 (reductive elimination from triplet diorgano-Ni^{III} complex associated to PhI radical anion)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	-1.556274	0.527575	-0.162122
2	6	0	-2.651385	2.095816	-0.226489
3	6	0	-4.711344	3.800083	0.637200
4	6	0	-3.946516	1.967269	-0.755641
5	6	0	-2.386636	3.118839	0.699154
6	6	0	-3.418973	3.950969	1.142037
7	6	0	-4.968805	2.807972	-0.314737
8	6	0	-1.048871	1.911209	-1.555365
9	7	0	-1.304158	-0.796031	1.278926
10	6	0	-1.239213	-2.835306	3.200869
11	6	0	-0.917854	-0.547246	2.553790
12	6	0	-1.696708	-2.084488	0.939672
13	6	0	-1.650924	-3.110068	1.915936
14	6	0	-0.865958	-1.507960	3.539385

```
   15          7             0       -2.138830   -1.111634   -1.191215
   16          6             0       -2.905785   -3.555956   -2.315762
   17          6             0       -2.517522   -1.195634   -2.483219
   18          6             0       -2.127775   -2.260198   -0.418518
   19          6             0       -2.516651   -3.494997   -0.995517
   20          6             0       -2.909035   -2.370590   -3.092985
   21          1             0       -5.509666    4.456571    0.972211
   22          1             0       -4.159651    1.199173   -1.493433
   23          1             0       -1.379160    3.268582    1.080852
   24          1             0       -3.205607    4.725619    1.874735
   25          1             0       -5.971940    2.687299   -0.716839
   26          1             0       -0.376932    1.120522   -1.925792
   27          1             0       -0.458954    2.740599   -1.165135
   28          1             0       -1.685501    2.250494   -2.370412
   29          1             0       -1.207510   -3.623865    3.947039
   30          1             0       -0.638543    0.482499    2.763880
   31          1             0       -1.951475   -4.117665    1.648100
   32          1             0       -0.543417   -1.246961    4.541450
   33          1             0       -3.202750   -4.503732   -2.755646
   34          1             0       -2.498405   -0.259927   -3.037381
   35          1             0       -2.503163   -4.397018   -0.392830
   36          1             0       -3.206752   -2.375172   -4.136016
   37         53             0        2.355845   -0.226888    0.202427
   38          6             0        4.389877    0.316882   -0.216663
   39          6             0        7.027152    1.024369   -0.759709
   40          6             0        5.271410    0.541511    0.840705
   41          6             0        4.807900    0.440551   -1.541542
   42          6             0        6.133064    0.796028   -1.806916
   43          6             0        6.593867    0.896076    0.560824
   44          1             0        8.056291    1.300273   -0.971640
   45          1             0        4.938482    0.442344    1.868381
   46          1             0        4.116221    0.262181   -2.358006
   47          1             0        6.461948    0.892897   -2.838221
   48          1             0        7.283384    1.071148    1.382452
 ---------------------------------------------------------------------

 Zero-point correction=                           0.375170
(Hartree/Particle)
 Thermal correction to Energy=                    0.401426
 Thermal correction to Enthalpy=                  0.402370
 Thermal correction to Gibbs Free Energy=         0.307312
 Sum of electronic and zero-point Energies=          -1178.852547
 Sum of electronic and thermal Energies=             -1178.826292
 Sum of electronic and thermal Enthalpies=           -1178.825348
 Sum of electronic and thermal Free Energies=        -1178.920406

-----------------------------------------------------------------------
 Variational PCM results
 =======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -1179.224175
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -1179.239641
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -1179.214620
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent               (kcal/mol) =      -9.71
 ---------------------------------------------------------------------
 Cavitation energy                        (kcal/mol) =      46.28
 Dispersion energy                        (kcal/mol) =     -33.03
 Repulsion energy                         (kcal/mol) =       2.45
 Total non electrostatic                  (kcal/mol) =      15.70
 ---------------------------------------------------------------------
```

IV. Coordinates and energies for the stationary points included in the main text for the cross-coupling of alkyl electrophiles with alkylzinc halides

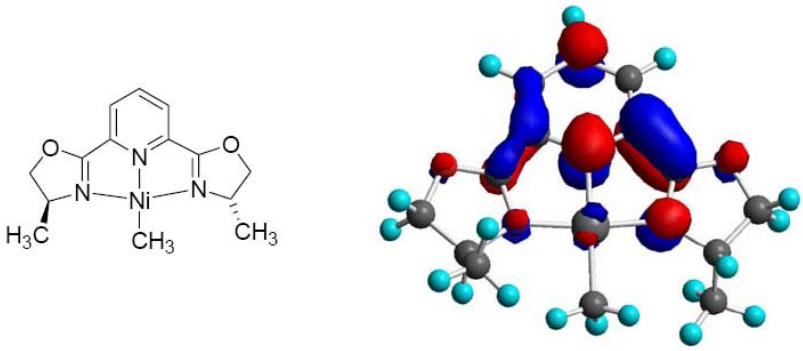


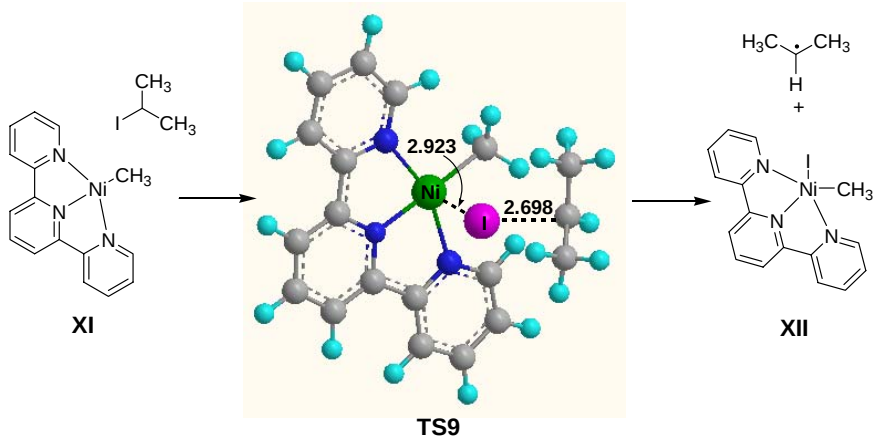
Figure for complex **(Me-Pybox)NiMe** *showing the ligand-centered single occupied molecular orbital.*

(Me-Pybox)NiMe

```
 Zero-point correction=                                 0.306800
(Hartree/Particle)
 Thermal correction to Energy=                    0.326107
 Thermal correction to Enthalpy=                  0.327051
 Thermal correction to Gibbs Free Energy=         0.258803
 Sum of electronic and zero-point Energies=          -1028.030883
 Sum of electronic and thermal Energies=             -1028.011577
 Sum of electronic and thermal Enthalpies=           -1028.010633
 Sum of electronic and thermal Free Energies=        -1028.078880

---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0       -0.015129   -0.726435    0.032025
    2          7             0       -0.020972    1.097959    0.304284
    3          6             0        0.060355    3.770172   -0.181725
    4          6             0       -1.180700    1.713575   -0.063476
    5          6             0        1.218712    1.699953    0.256128
    6          6             0        1.248270    3.110764    0.060004
    7          6             0       -1.182011    3.089792   -0.283626
    8          1             0        2.205776    3.638073    0.085269
    9          1             0       -2.097209    3.626544   -0.544161
   10          1             0        0.064420    4.855274   -0.328558
   11          7             0        1.845787   -0.634647    0.200438
   12          6             0        3.116571   -1.459497    0.207109
   13          6             0        4.203921   -0.374445    0.356051
   14          8             0        3.549743    0.903146    0.350272
   15          6             0        2.197459    0.683348    0.264446
   16          1             0        3.105177   -2.147974    1.087350
   17          1             0        4.763939   -0.435841    1.304122
   18          1             0        4.930735   -0.353005   -0.473844
   19          7             0       -1.873528   -0.615911   -0.118647
```

20	6	0	-3.149436	-1.435724	-0.134380
21	6	0	-4.222502	-0.342246	-0.325222
22	8	0	-3.538060	0.926213	-0.332656
23	6	0	-2.203066	0.682127	-0.189222
24	1	0	-3.130634	-2.149394	-0.995180
25	1	0	-4.764566	-0.409517	-1.282988
26	1	0	-4.961422	-0.294572	0.492946
27	6	0	3.279846	-2.265754	-1.067369
28	1	0	4.313684	-2.622334	-1.170065
29	1	0	3.039120	-1.680242	-1.965481
30	1	0	2.629429	-3.151427	-1.072137
31	6	0	-3.312208	-2.200339	1.165835
32	1	0	-4.314914	-2.644448	1.223693
33	1	0	-3.182700	-1.554371	2.045639
34	1	0	-2.584766	-3.019946	1.256194
35	6	0	0.020447	-2.649320	-0.394760
36	1	0	0.344702	-2.787264	-1.432568
37	1	0	-0.983177	-3.070637	-0.266515
38	1	0	0.719609	-3.159847	0.277364



Activation free energy of 5.1 kcal mol^{-1}, the reaction is exoergic (-7.3 kcal mol^{-1}). Scheme includes the geometry of the **TS9**, in which specified distances are in Å.

Ni_tpy_Me

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	-0.004264	-1.041783	0.028262
2	7	0	-1.935088	-0.746441	-0.006846
3	6	0	-4.644393	-0.005308	-0.047838
4	6	0	-2.303591	0.589505	-0.001044
5	6	0	-2.914252	-1.674045	-0.043132
6	6	0	-4.262730	-1.359282	-0.065328
7	6	0	-3.656067	0.963608	-0.016490
8	7	0	0.009326	0.844610	0.011185
9	6	0	0.024617	3.593027	0.022311
10	6	0	1.207381	1.494547	0.013705
11	6	0	-1.181597	1.508630	0.010825
12	6	0	-1.196355	2.901025	0.016715

13	6	0	1.237127	2.887303	0.020184
14	7	0	1.938645	-0.771306	-0.008238
15	6	0	4.656905	-0.043850	-0.044181
16	6	0	2.915702	-1.700863	-0.050000
17	6	0	2.318388	0.563020	0.002404
18	6	0	3.673461	0.929169	-0.009580
19	6	0	4.266397	-1.394940	-0.069810
20	6	0	-0.089685	-2.969731	0.123359
21	1	0	-5.692818	0.277237	-0.061225
22	1	0	-2.581692	-2.704457	-0.053641
23	1	0	-4.999376	-2.155016	-0.095616
24	1	0	-3.916029	2.017347	-0.006779
25	1	0	0.030858	4.678327	0.026703
26	1	0	-2.133646	3.448425	0.016998
27	1	0	2.180207	3.424618	0.023087
28	1	0	5.706893	0.232912	-0.054671
29	1	0	2.581910	-2.729966	-0.068767
30	1	0	3.938758	1.981494	0.005060
31	1	0	4.997270	-2.195782	-0.104295
32	1	0	-0.495895	-3.366580	-0.819228
33	1	0	-0.764368	-3.252822	0.943571
34	1	0	0.869310	-3.464751	0.312176

Zero-point correction=	0.264467
(Hartree/Particle)	
Thermal correction to Energy=	0.280902
Thermal correction to Enthalpy=	0.281847
Thermal correction to Gibbs Free Energy=	0.219375
Sum of electronic and zero-point Energies=	-951.455577
Sum of electronic and thermal Energies=	-951.439142
Sum of electronic and thermal Enthalpies=	-951.438197
Sum of electronic and thermal Free Energies=	-951.500668

2-Iodopropane

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.135659	2.017382	-0.369621
2	6	0	0.225530	1.340360	-0.364099
3	53	0	-0.042716	-0.862831	0.002920
4	6	0	1.194585	1.905501	0.661947
5	1	0	-0.997114	3.084768	-0.594493
6	1	0	-1.625134	1.938545	0.606291
7	1	0	-1.800714	1.593817	-1.126609
8	1	0	0.667013	1.335750	-1.361880
9	1	0	2.164967	1.403506	0.628830
10	1	0	0.794746	1.822240	1.677526
11	1	0	1.353471	2.971939	0.446214

Zero-point correction=	0.094325
(Hartree/Particle)	
Thermal correction to Energy=	0.099891
Thermal correction to Enthalpy=	0.100835
Thermal correction to Gibbs Free Energy=	0.064138

```
 Sum of electronic and zero-point Energies=          -129.831260
 Sum of electronic and thermal Energies=             -129.825694
 Sum of electronic and thermal Enthalpies=           -129.824750
 Sum of electronic and thermal Free Energies=        -129.861447
```

XI

```
 Zero-point correction=                           0.356799
(Hartree/Particle)
 Thermal correction to Energy=                    0.380404
 Thermal correction to Enthalpy=                  0.381349
 Thermal correction to Gibbs Free Energy=         0.298076
 Sum of electronic and zero-point Energies=          -1081.264918
 Sum of electronic and thermal Energies=             -1081.241312
 Sum of electronic and thermal Enthalpies=           -1081.240368
 Sum of electronic and thermal Free Energies=        -1081.323641

---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28              0       -0.517071    0.025979    1.328847
    2          6              0        0.670324   -0.102918    2.939249
    3          1              0        0.080399   -0.008401    3.864765
    4          1              0        1.433739    0.688585    2.965933
    5          1              0        1.203676   -1.062577    2.999918
    6          7              0       -0.696316    2.161646    1.030527
    7          6              0       -1.058646    4.853625    0.399539
    8          6              0       -1.508865    2.514909   -0.014154
    9          6              0       -0.086653    3.123661    1.742390
   10          6              0       -0.231039    4.476182    1.473777
   11          6              0       -1.695348    3.872815   -0.340989
   12          7              0       -1.811316    0.165156   -0.207580
   13          6              0       -3.565874    0.358956   -2.355729
   14          6              0       -2.359125   -0.972698   -0.744121
   15          6              0       -2.138350    1.399414   -0.710414
   16          6              0       -3.012828    1.514340   -1.788477
   17          6              0       -3.237354   -0.894467   -1.822017
   18          7              0       -1.078151   -2.036814    0.964254
   19          6              0       -1.929156   -4.597529    0.260383
   20          6              0       -0.652553   -3.114690    1.643100
   21          6              0       -1.944477   -2.204970   -0.082902
   22          6              0       -2.377669   -3.495225   -0.446825
   23          6              0       -1.043028   -4.409510    1.337209
   24          1              0       -1.199831    5.902169    0.152823
   25          1              0        0.538630    2.770810    2.557447
   26          1              0        0.283136    5.213870    2.080839
   27          1              0       -2.338426    4.148184   -1.170232
   28          1              0       -4.248259    0.434383   -3.196208
   29          1              0       -3.270572    2.489132   -2.189185
   30          1              0       -3.670024   -1.793249   -2.248954
   31          1              0       -2.260737   -5.594837   -0.014677
   32          1              0        0.028880   -2.907387    2.463101
   33          1              0       -3.062663   -3.623289   -1.278229
   34          1              0       -0.669993   -5.246419    1.918188
   35          6              0        5.044256   -0.110439   -1.261571
   36          6              0        3.957285    0.009870   -0.205324
   37          6              0        4.051510   -1.019849    0.908276
```

38	1	0	5.036478	-1.098704	-1.732550
39	1	0	6.021265	0.025482	-0.776140
40	1	0	4.944058	0.647854	-2.042732
41	1	0	3.910734	1.022300	0.198501
42	1	0	3.250906	-0.900405	1.642049
43	1	0	5.014006	-0.889930	1.424149
44	1	0	4.015654	-2.040017	0.512061
45	53	0	1.947980	-0.153656	-1.196932

TS9

Zero-point correction= 0.355423
(Hartree/Particle)
Thermal correction to Energy= 0.379783
Thermal correction to Enthalpy= 0.380727
Thermal correction to Gibbs Free Energy= 0.296193
Sum of electronic and zero-point Energies= -1081.256210
Sum of electronic and thermal Energies= -1081.231850
Sum of electronic and thermal Enthalpies= -1081.230906
Sum of electronic and thermal Free Energies= -1081.315440

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	0.035031	-0.641498	-0.986705
2	6	0	-0.088624	0.055268	-2.854307
3	1	0	-0.024716	-0.767271	-3.585245
4	1	0	0.719847	0.764966	-3.076834
5	1	0	-1.033279	0.587169	-3.031906
6	7	0	2.189929	-0.867172	-0.683696
7	6	0	4.876666	-1.143454	-0.013054
8	6	0	2.541413	-1.529355	0.449868
9	6	0	3.146184	-0.354423	-1.468830
10	6	0	4.501573	-0.466138	-1.179932
11	6	0	3.890780	-1.677433	0.806554
12	7	0	0.190179	-1.778207	0.727933
13	6	0	0.395584	-3.218559	3.085400
14	6	0	-0.935137	-2.237812	1.334249
15	6	0	1.416578	-2.050137	1.244030
16	6	0	1.546513	-2.766522	2.434300
17	6	0	-0.858512	-2.958993	2.526386
18	7	0	-2.031016	-1.185644	-0.511017
19	6	0	-4.581785	-1.878777	0.361338
20	6	0	-3.114536	-0.823902	-1.210805
21	6	0	-2.185633	-1.899840	0.635282
22	6	0	-3.463587	-2.256536	1.093193
23	6	0	-4.409000	-1.146086	-0.819725
24	1	0	5.924467	-1.251567	0.252139
25	1	0	2.792190	0.161998	-2.355535
26	1	0	5.240151	-0.034289	-1.847168
27	1	0	4.164878	-2.202094	1.715292
28	1	0	0.475722	-3.775852	4.013391
29	1	0	2.524396	-2.978453	2.852036
30	1	0	-1.755592	-3.320268	3.016740
31	1	0	-5.576071	-2.149167	0.705069
32	1	0	-2.916042	-0.253423	-2.112726
33	1	0	-3.580525	-2.821117	2.011714
34	1	0	-5.255845	-0.830910	-1.420333

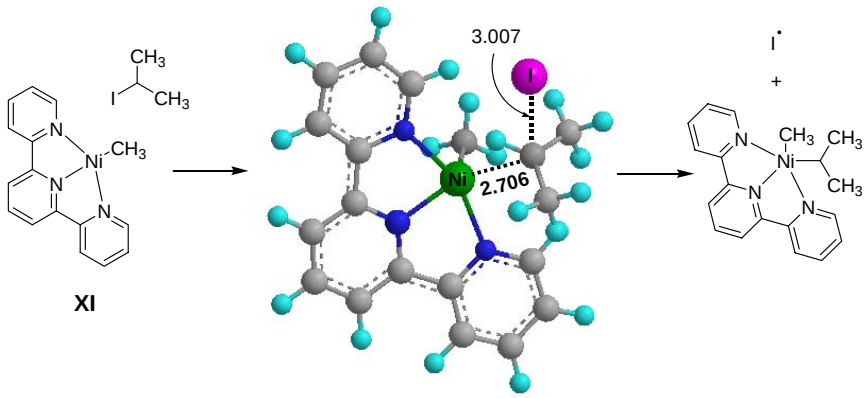
35	6	0	0.340316	4.925928	1.836900
36	6	0	-0.091035	4.470579	0.475045
37	6	0	-1.466120	4.834121	0.002625
38	1	0	-0.394001	4.656350	2.605029
39	1	0	0.437697	6.026802	1.855098
40	1	0	1.308620	4.504086	2.121652
41	1	0	0.683183	4.478524	-0.288746
42	1	0	-1.712418	4.346832	-0.945142
43	1	0	-1.537383	5.925978	-0.153285
44	1	0	-2.230479	4.563249	0.740073
45	53	0	-0.100827	1.778473	0.647574

XII

Zero-point correction= 0.354433
(Hartree/Particle)
Thermal correction to Energy= 0.379945
Thermal correction to Enthalpy= 0.380889
Thermal correction to Gibbs Free Energy= 0.289353
Sum of electronic and zero-point Energies= -1081.270241
Sum of electronic and thermal Energies= -1081.244728
Sum of electronic and thermal Enthalpies= -1081.243784
Sum of electronic and thermal Free Energies= -1081.335320

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	28	0	-0.036851	-0.825359	-0.791912
2	6	0	-0.253860	0.029326	-2.582842
3	1	0	-0.273242	-0.735516	-3.377568
4	1	0	0.563337	0.727612	-2.805632
5	1	0	-1.187287	0.603956	-2.640378
6	7	0	2.149886	-1.061038	-0.582495
7	6	0	4.860177	-1.373935	-0.065765
8	6	0	2.558060	-1.920526	0.374833
9	6	0	3.055315	-0.360558	-1.269266
10	6	0	4.426695	-0.482488	-1.045111
11	6	0	3.916401	-2.103640	0.654578
12	7	0	0.228554	-2.342313	0.675559
13	6	0	0.559703	-4.110353	2.756749
14	6	0	-0.853937	-2.898547	1.240374
15	6	0	1.468931	-2.628915	1.099858
16	6	0	1.672152	-3.524950	2.156087
17	6	0	-0.720347	-3.801848	2.301387
18	7	0	-2.068975	-1.557138	-0.333137
19	6	0	-4.554985	-2.479620	0.492007
20	6	0	-3.185022	-1.099731	-0.905421
21	6	0	-2.154020	-2.470992	0.656726
22	6	0	-3.391287	-2.957810	1.091309
23	6	0	-4.455558	-1.531626	-0.524475
24	1	0	5.919086	-1.499814	0.140349
25	1	0	2.654058	0.320382	-2.012884
26	1	0	5.128282	0.110413	-1.622468
27	1	0	4.238550	-2.798223	1.422211
28	1	0	0.690047	-4.803801	3.582183
29	1	0	2.668738	-3.758586	2.511756

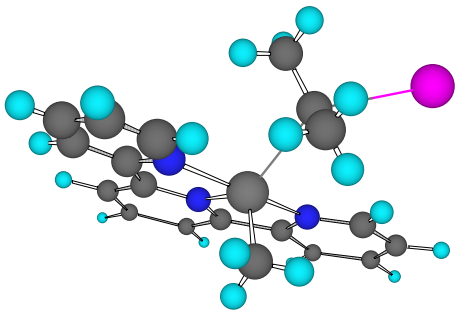
30	1	0	-1.587860	-4.251103	2.770259
31	1	0	-5.524924	-2.842862	0.818951
32	1	0	-3.041219	-0.359977	-1.686218
33	1	0	-3.452849	-3.693885	1.885023
34	1	0	-5.337136	-1.129128	-1.012246
35	6	0	-0.142361	6.562483	1.922370
36	6	0	-0.245641	5.799534	0.642732
37	6	0	-0.800068	6.437886	-0.588098
38	1	0	-1.129613	6.720206	2.396894
39	1	0	0.281800	7.565873	1.765659
40	1	0	0.480491	6.040415	2.657699
41	1	0	-0.151909	4.716490	0.671337
42	1	0	-0.602969	5.835567	-1.482305
43	1	0	-0.379014	7.441510	-0.751522
44	1	0	-1.897012	6.573424	-0.531747
45	53	0	-0.168065	1.228428	1.053645



XI **TS10**

TS10 is 10.2 kcal mol^{-1} less stable than **TS9**. Scheme includes the geometry of **TS10**, in which specified distances are in Å.

Transition state for the reaction of (tpy)NiMe with 2-iodopropane releasing atomic iodine (TS10):



```
 Zero-point correction=                                  0.355177
(Hartree/Particle)
 Thermal correction to Energy=                    0.380824
 Thermal correction to Enthalpy=                  0.381769
 Thermal correction to Gibbs Free Energy=         0.292318
 Sum of electronic and zero-point Energies=          -1081.236351
 Sum of electronic and thermal Energies=             -1081.210703
 Sum of electronic and thermal Enthalpies=           -1081.209759
 Sum of electronic and thermal Free Energies=        -1081.299209
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         28             0        0.636498   -0.401846    0.176607
    2          7             0        0.595625    0.117324   -1.937596
    3          6             0        0.159745    0.588910   -4.645438
    4          6             0       -0.656427    0.385355   -2.388172
    5          6             0        1.614293    0.094417   -2.807883
    6          6             0        1.444415    0.327664   -4.171518
    7          6             0       -0.902723    0.619725   -3.745156
    8          7             0       -1.272738    0.145024   -0.097122
    9          6             0       -3.918204    0.815729   -0.478341
   10          6             0       -2.098504    0.212729    0.975873
   11          6             0       -1.706990    0.430747   -1.345562
   12          6             0       -3.041674    0.767346   -1.568835
   13          6             0       -3.446632    0.546435    0.804542
   14          7             0       -0.123661   -0.376253    2.194523
   15          6             0       -1.409191   -0.285276    4.668232
   16          6             0        0.542573   -0.645237    3.326792
   17          6             0       -1.447830   -0.064330    2.266077
   18          6             0       -2.110687   -0.009614    3.501649
   19          6             0       -0.050240   -0.612882    4.583654
   20          6             0        1.042717   -2.356692   -0.017771
   21          1             0       -0.015215    0.774246   -5.701094
   22          1             0        2.601803   -0.088192   -2.396334
   23          1             0        2.305588    0.315199   -4.830263
   24          1             0       -1.907461    0.826114   -4.096573
   25          1             0       -4.961304    1.074007   -0.631512
   26          1             0       -3.400404    0.999129   -2.564766
   27          1             0       -4.119647    0.598870    1.652759
   28          1             0       -1.911334   -0.246399    5.630212
   29          1             0        1.591683   -0.897625    3.207714
   30          1             0       -3.163311    0.246787    3.548722
   31          1             0        0.534652   -0.840744    5.468303
   32          1             0        1.853053   -2.487360   -0.745102
   33          1             0        0.146357   -2.872750   -0.379575
   34          1             0        1.341130   -2.779249    0.948610
   35          6             0        2.622133    2.104634    1.613176
   36          6             0        2.912795    0.973562    0.676517
   37          6             0        3.841188   -0.125070    1.096418
   38          1             0        3.553260    2.593766    1.929674
   39          1             0        2.123968    1.753242    2.532333
   40          1             0        1.989059    2.864919    1.147242
   41          1             0        2.454198    0.964764   -0.302019
   42          1             0        3.469861   -0.656481    1.988724
   43          1             0        4.823682    0.284243    1.366951
   44          1             0        3.992046   -0.861676    0.303587
   45         53             0        4.638857    2.294787   -1.401258
```